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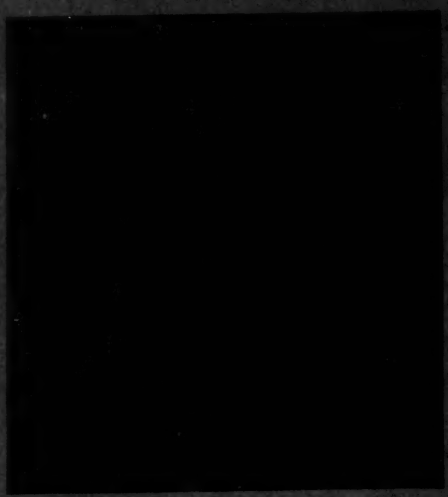

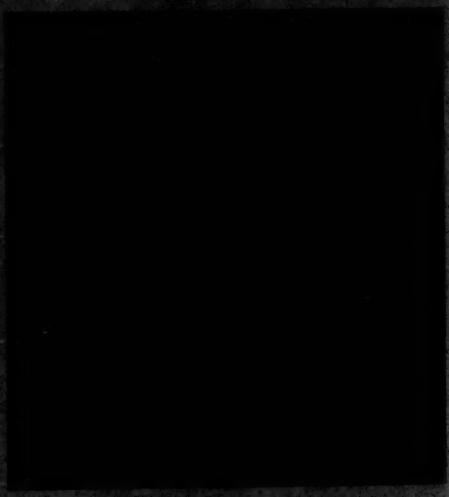

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THE BRITISH JOURNAL

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OPHTHALMOLOGY

JANUARY, 1950

COMMUNICATIONS

ELECTRORETINOGRAPHY OF EXPERIMENTAL ANIMALS*

BY

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ELECTRORETINOGRAPHY affords the only truly objective method of assessing retinal function in animals, since active co-operation on the part of an experimental animal is not obtainable in the same way as from a human subject. Electroretinographic records of many different animals have been published (*e.g.*, human, Adrian 1945; Karpe 1945, 1948; rat, Charpentier 1936; cat, monkey, pigeon, Adrian 1946; frog, Granit and Riddell 1934; insects, Jahn and Wolff 1941). It is the purpose of this paper to discuss the method as a routine examination of experimental animals and to describe the results obtained using a simple condenser-coupled amplifier, cathode ray tube and photographic recorder. Normal guinea-pigs and pigeons and normal and vitamin A-deficient rabbits have been used.

* Received for publication, July 8, 1949.

The main difficulty in recording the electrical response of the retina is to keep the animal quiet. It is essential that the animal be kept comfortable and the instrument described here was designed with this particular end in view. The result is that the recording of the retinal response is now a relatively simple procedure which can be carried out repeatedly on the same animal. The design of the amplifier, light stimulator and electrodes and the method of anaesthetising and handling the animal are described in some detail in the hope that the simplifications introduced may be useful to others.

A detailed account of the history of electroretinography and of the analysis of the resulting records has been given by Granit (1947). The basic principle consists in leading off the electrical potential from the eye (usually from the cornea with reference to a point on the body as near the back of the eye as possible) to be amplified and recorded on paper or on film.

METHODS

The amplifier.—The design of equipment of this kind depends entirely on the nature of the phenomena to be recorded. When using light stimuli lasting one second or longer the amplifier must be capable of maintaining the wave form faithfully for at least two seconds and direct coupling of the stages is essential, but when flash stimuli are used (0·1 second, or less) and the response from the eye does not last above 0·5 second, condenser coupling can be used, greatly simplifying construction. The magnitude of the input is important. The response from the eye, in most animals, is between 0·05 and 0·5 mV., usually about 0·2 mV. Since a cathode ray tube needs an input of 20-100 V. to produce a good deflection, the amplifier must have a gain of at least 10^5.

This means that there is a great possibility of interference being picked up from outside, especially 50 cycle hum from mains operated equipment and the input must therefore be screened. A cage built of expanded metal fastened to a wooden framework $6\frac{1}{2}$ x 5 x 4 ft. and fitted with a door is suitable. All joints in the expanded metal are securely soldered and the whole bonded to a cold water main. A standard amplifier rack $3\frac{1}{2}$ ft. high is fitted into this cage and this houses the batteries, pre-amplifiers and calibrator and also serves as a bench on which the animal and stimulator rest during the experiment.

A resistance capacity coupled amplifier has been built for this work and the circuit is shown in Fig. 3. To obtain sufficient gain to drive a cathode ray tube several stages are necessary. A three stage amplifier in conjunction with a compressor circuit described

by Tönnies (1938) and Saunders (1942) has been used to minimise the effect of stray pick-up from the leads and the animal and also the effect of potentials derived from heart-beats and respiration. The calibrator network is contained within a metal screen inside the compressor unit and can be switched in and out of circuit as required without disturbing the connections to the animal. The calibrator is tapped to give 0·02, 0·2, and 2·0 mV. Normally only the 0·2 mV tapping is used. Coupling condensers and grid and anode resistors are made as large as possible throughout the amplifier to maintain a high time-constant. With the values shown in Fig. 3 a constant input gives an output falling to half maximum in about 0·4 seconds.

Recordings are made on 35 mm. recording paper in a Cossor model 427 camera with a film speed of 1 cm./second. Sweep circuits are not used for recording electroretinograms. The compressor input stage and battery operated pre-amplifier stage are kept within the screening cage and are connected to the mains operated stages and recording gear outside the cage by means of screened cables. The camera and motor can be operated from within the cage by mechanical arrangement so that no interference is introduced from this source.

The light stimulator.—The arrangement is set out diagrammatically in Fig. 1. The light source is a 6v. 30w. V-filament car headlamp bulb fitted in an adapted gunsight. The current flowing

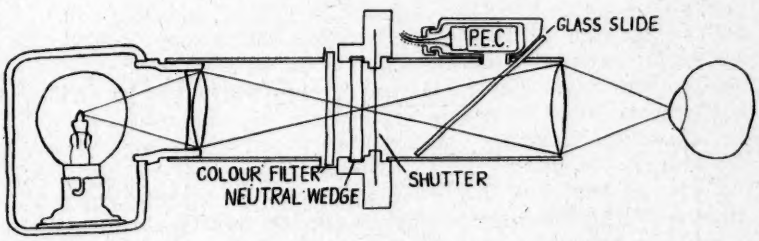

FIG. 1.

The light stimulator. The lamp is a 6v. 30w. car headlamp bulb with the current controlled at 5 amps. Colour temperature 2950-3000° K.

through the lamp is controlled at 5 amps., maintaining a fairly constant colour temperature of 2950-3000° K. (maker's data). Light from the bulb is focused on to a sliding neutral density optical wedge and a spring loaded shutter giving flashes lasting about 0·1 second. A second lens is used to focus the light on to the pupil of the eye being examined. Provision is also made for

the introduction of colour filters and a photo-electric cell is fitted which can be used to signal the light flash on the second beam of the oscilloscope.

The comfort of the animal is so important for getting clear records with a quiet background that the light stimulator has been designed as a movable unit so that it can be adjusted to suit the position of the animal. The adapting light is also movable.

The electrodes.—The usual type of electrode for electroretinogram recording is a U tube filled with saline or Ringer solution having a silver rod coated with silver chloride dipping into one

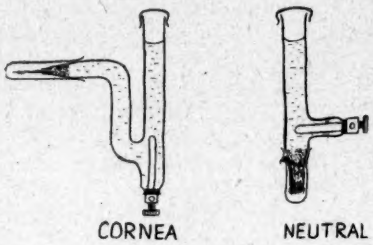

FIG. 2.

Design of electrodes. The cotton wicks are held in place by packed cotton wool.

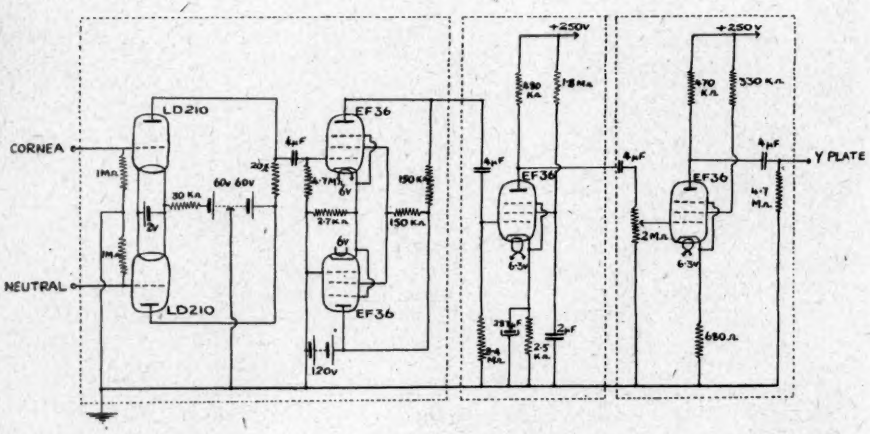

FIG. 3.

Circuit of amplifier. Mains operated power units for the last two stages and for the C.R.T. are not shown.

arm. Contact with the eye is made by a cotton wick soaked in the solution and leading from the other arm. This arrangement is very simple and works quite well but when working in the dark trouble arises from fluid siphoning unnoticed along the wick. Care is needed in using closed electrodes because peculiar and varying potential changes may arise from air bubbles in contact with the silver rod. I have found the type of electrode shown in Fig. 2 the most satisfactory in use. Different designs are used for the corneal and indifferent electrodes to minimise the possibility of air bubbles coming into contact with the silver rods in the different positions. Rubber caps taken from vaccine phials are used to close the ends of the tubes, so that saline may be added with a hypodermic needle through the rubber while the electrode is in position. Small glass caps ground to cover the tubes holding the wicks prevent drying of the electrodes when not in use.

The silver is re-coated with silver chloride before each experiment by connecting the electrode to the positive terminal of a 4v. battery while the cotton wick dips into a dish of saline containing a platinum foil electrode connected to the negative terminal. Current is left running for about half an hour. If this is not done before each experiment, spurious potentials are likely to arise due to polarisation and these will disturb the base-line.

THE EXPERIMENTAL ANIMAL

Choice of anaesthetic.—Inhalation anaesthetics, such as ether, chloroform and anaesthetics inducing anoxia, such as nitrous oxide, depress the response and alter its character as well as being difficult to administer while a record is being taken. Chloralose has a similar effect on the response. Avertin and urethane are in some ways excellent anaesthetics, but, in our hands, the casualty rate was high and if the animals are required to survive, these anaesthetics are not recommended. Nembutal anaesthesia has given the best results for routine work where several observations have to be made on the same animal over a period of time. It may be short acting if the animal is uncomfortable and for this reason animal holding boxes of the guillotine type should not be used. A comfortable animal will remain quiet for up to an hour, sometimes even longer, under Nembutal. In cold weather the animal should lie on an electrically heated pad for greater comfort. Both eyes should be cocainised as animals sometimes become restless while lying on an opened eye under the anaesthetic.

Rabbits are given 0·5 ml. Nembutal (Abbott) per kilogram body weight into the marginal ear vein. Pigeons were found to possess

a strong blink reflex, especially from the third lid, which could not be abolished by a general anaesthetic without risk of killing the birds. These blinks give rise to large negative action currents which could swamp the electroretinogram record. They can, however, be abolished by a retrobulbar injection of procaine hydrochloride. An injection under the skin round the eye was of no use and neither was curare in conjunction with light Nembutal. For routine electroretinographic measurements pigeons were given about 0·2 ml. Nembutal (depending on weight) into the wing vein and 0·2-0·3 ml. procaine hydrochloride 4 per cent. w./v. solution with adrenalin (B.P.) into the orbit. Because of the shape of the pigeon's eye great care is needed not to puncture the globe when giving this retrobulbar injection.

Animal holder.—Each species provides its own difficulties. The method of holding varies with the animal and no universal holder has been found. Rabbits are wrapped in an electrically heated blanket (6v., 3w.) after anaesthetisation and left to lie on the bench while the stimulator and electrodes are adjusted to suit the position of the animal. One electrode is applied to a shaved spot on the top of the head, contact being aided by addition of a wetting agent, such as " Drene " shampoo, to the saline. The second electrode is applied to the cornea without a wetting agent.

A small speculum, illustrated in Fig. 4, made from 30-gauge steel wire is used to hold the lids apart during the experiment. If

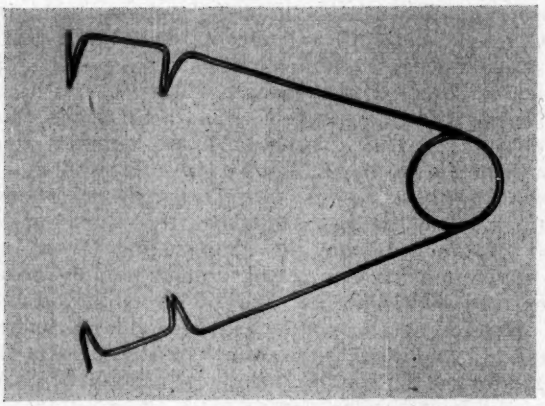

FIG. 4.

Miniature speculum made from 30 s.w.g. spring steel. For pigeons these are made 1·5-2·0 cm. long, and for rabbits about 2·5 cm. long.

this speculum is earthed to the amplifier chassis stray interference can be greatly reduced. Karpe (1949) dispenses with the screening cage entirely in his clinical work, using only an earthed speculum.

A special holder was made for pigeons and is shown in Fig. 5. A block of plastic material was shaped to fit the beak and hold the head firmly with the neck supported in a hole in the top of the

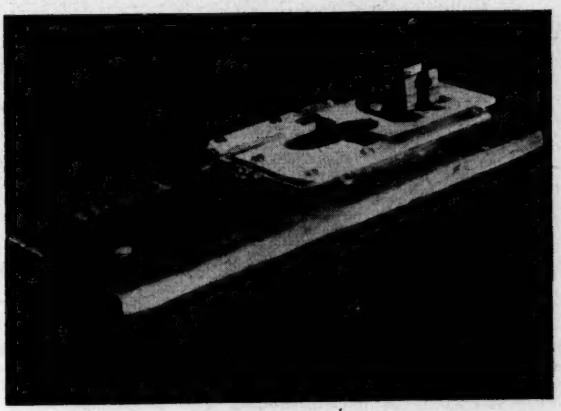

FIG. 5.

Holder for pigeons. The bird's neck and head protrude through the hole in the lid while its beak is held lightly in the plastic block to the right. The box is 23 cm. × 11 cm. × 9 cm. and is open at both ends.

box. The pigeon's body is held wrapped in an electrically heated blanket inside the box. The holder was designed to suit a natural position of the bird.

Production of vitamin A deficiency. — Rabbits were fed the vitamin A-deficient diet described by Mann, Pirie, Tansley and Wood (1946). The course of the deficiency was assessed by weight records, slit lamp examination of the eyes and estimation of liver vitamin A levels.

RESULTS

Specimen records from different animal species are given to show the performance of the instrument described. These results confirm and expand those of previous workers.

I. *The response to white light*

The records from a normal pigeon, guinea pig and rabbit are shown in Fig. 6. The guinea pig record shows also the signal

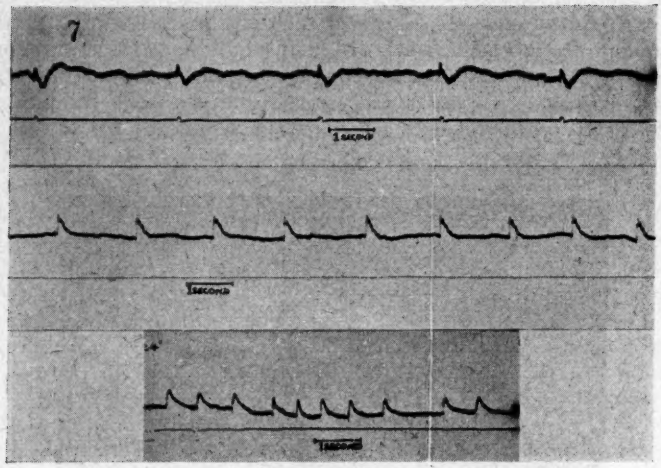

FIG. 6.

Top. Record from normal guinea pig. Middle. Record from normal pigeon. Bottom. Record from normal rabbit. Before the records were taken the animals had been exposed to normal room lighting. Stimulus was about ten times threshold.

from the light flash. In the others the light stimulus was too feeble to elicit a response from the photo-electric cell and no signal is seen. There is an interesting difference in the responses given by these species, perhaps the most interesting is the negative wave given by the guinea pig, also noticed by Boehm, Sigg and Monnier (1944). This kind of response was never obtained from either rabbits or pigeons. The overall amplitude of the response in each case was about 0·3 mV.

II. *The response to light of different wavelengths*

The records in Fig. 7 show quite clearly the difference in response to light of different wavelengths between the pigeon which is diurnal and has a retina composed mainly of cones and the rabbit which is nocturnal and has a largely rod retina. The stimulator was adjusted so that the same amount of light energy entered the eye in each case. The neutral wedge setting was calculated from the energy emitted by the lamp at the particular wavelength (Wein equation) and that transmitted by the colour filters (maker's data). The pigeon's eye was much more sensitive to the longer than to the shorter wavelengths, whereas the converse was true of the rabbit. These results are in agreement with those of Adrian (1946).

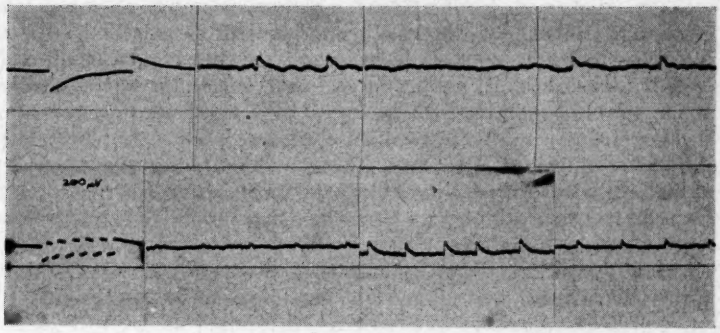

FIG. 7.

Response to different wavelengths. Upper pigeon, lower rabbit. Left to right. Calibration 200μv, red, blue, white, equal energy.

III. *Dark adaptation curves*

In addition to recording and measuring the response to a light stimulus well above the threshold, it has frequently been useful to determine the minimum stimulus required to elicit a response. In this case a particularly quiet background was necessary but distortion of the shape of the wave was of little consequence. All

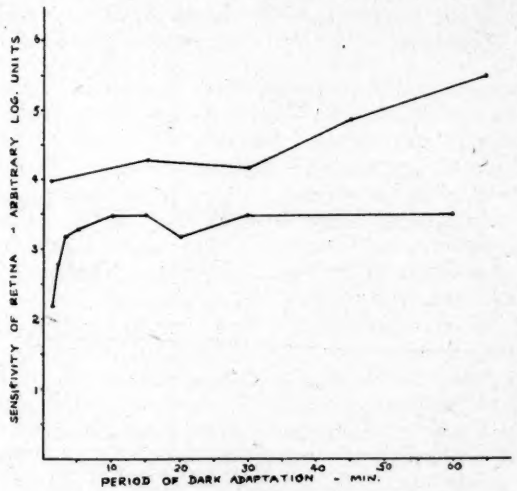

FIG. 8.

Dark adaptation curves of pigeon (upper) and rabbit (lower).

that was required was to know whether or not a response was obtained. Much of the background noise, especially high frequency valve noise, could be by-passed by means of a small condensor (say 0·002 μF) connected between the input to the oscilloscope amplifier and earth. Examples of dark adaptation curves of a pigeon and a rabbit plotted on the same scale using this technique are given in Fig. 8. The animal was light adapted by exposure to an open 36-watt bulb six inches from the eye for five minutes. Dark adaptation time was measured from the instant this adapting light was switched off. At intervals the minimum stimulus required to elicit a barely discernible response was measured and the wedge reading then gave the relative sensitivity of the retina expressed in arbitrary log units.

The rabbit showed a very rapid adaptation so that after five minutes or so the sensitivity remained more or less constant. The overall rise in sensitivity was about a hundredfold after the first half minute. The adaptation of the pigeon was much slower, little change being noticed until after thirty minutes adaptation. There was, however, a definite adaptation represented by an increase in sensitivity of 1·5 log units.

Vitamin A Deficiency

Seven rabbits were made vitamin A-deficient and dark adaptation curves plotted at intervals using the threshold technique. The sensitivity of the retina gradually decreased as the deficiency progressed. Expressed in arbitrary logarthmic units, this decrease

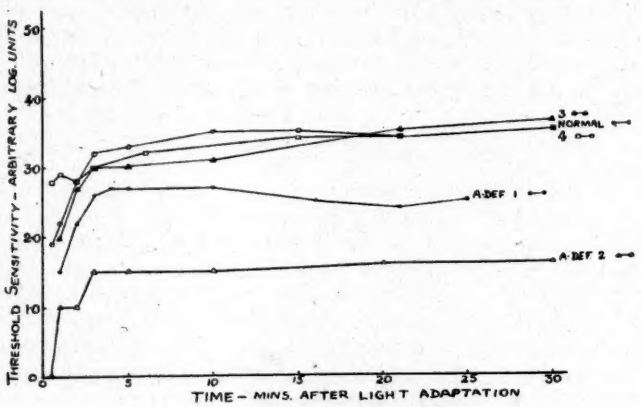

FIG. 9.

Dark adaptation curves in vitamin A deficiency in the rabbit (see text).

was generally from about 3·6, the normal value, to about 1·5 in the deficient state. The rabbits used in these investigations all showed the same general effect although frequently the variation found between one animal and another was as great as the differences found in any one animal during the course of the vitamin A deficiency. A typical set of curves obtained from one animal is shown in Fig. 9. The " normal " curve was obtained from a weanling rabbit at the time the deficient diet was started. Curve 1 was plotted five months later when slit-lamp observation showed slight migration of the limbal pigment, but no corneal change. Curve 2 was plotted five months after Curve 1. By this time the corneal lesions had become well advanced and the animal rather weak. Immediately after this curve was taken the animal was given 10,000 I.U. vitamin A concentrate; the dose was repeated twice more and on the third day Curve 3 was obtained. The corneae were again quite clear. Treatment with vitamin A concentrate was repeated at weekly intervals for two months longer and Curve 4 obtained.

Vitamin A concentration (Davies, 1933) in the livers of three animals killed during deficiency had fallen to 31 I.U. per gram (normal value 400 I.U. per gram ± 95; 11 observations).

DISCUSSION

General.—The technique described here was chosen after consideration of the published alternatives and a discussion of the reasons governing the choice may be useful.

The electrical method of assessing visual function can only provide information about retinal activity. *It does not tell us what the animal actually sees.* For example, it has been shown (Granit, 1945) that the cat retina contains hue-discriminating elements, whereas the animal as a whole is almost certainly colour blind. The retina is only one link in the visual system so that training experiments alone can provide information as to what the animal sees, since " seeing " involves not only the production of impulses in the optic nerve, but also an interpretation of these impulses by the animal's higher centres. Such training methods are, however, extremely tedious and time-consuming and, unless in expert hands, of little value. Where one's attention is confined to the physiology of the retina, electroretinography is the method of choice. It is rapid, a number of observations may be carried out on the same animal, the personal factor is practically eliminated and the method does give a truly objective indication of retinal activity independent of psychic or other sensory mechanisms.

Amplifiers.—A direct coupled amplifier is necessary if prolonged

stimuli are to be used. Several circuits have been published which are claimed to give good results (*e.g.*, Leksell, 1939; Matthews, 1938; Goodwin, 1941). If the recording device is capable of being operated by a push-pull circuit this type is recommended because it seems to be less susceptible to base-line drift than is the asymmetrical type. A double-beam oscilloscope needs a single-ended input so that in this case it would be better to use a compressor stage (Matthews, 1938). Capacitance in the batteries used for coupling may be troublesome if rapid changes are to be recorded, as in the case of nerve action potentials, but this can be reduced somewhat by the use of small batteries of the " deaf aid " type. These batteries are quite suitable in these positions since no current is taken from them and their life in the amplifier is almost equal to their shelf-life.

For general work, however, the resistance capacity coupled amplifier is much easier to handle and is the type I use. There are many designs and circuits published (Parnum, 1945; Parr and Walter, 1943), some of which employ push-pull operation and others single-ended circuits. My experience is that the amplifier should be kept as simple as possible—sliding contact gain controls and variable coupling and by-pass condensers should be avoided as far as possible because sooner or later the contacts give trouble. Each section should be built as a separate screened unit connected by short screened leads to avoid feed-back, which would cause the amplifier to oscillate, and to avoid interference pick-up.

Interference may arise within the instrument itself, though with a carefully constructed amplifier properly screened little trouble should arise from this source. A source of interference which arose in the early part of this work and proved difficult to locate at the time was an increase in internal resistance of the H.T. batteries in the pre-amplifier stages. Although the voltage had not decreased appreciably when tested with a meter, considerable noise appeared when the calibrator was not in use. For some time the noise was attributed to the electrodes, but when the batteries were replaced clear records were again obtained.

Light stimulator.—Both Karpe (1945) and Adrian (1946) used a large illuminated opal screen as a light stimulus rather than a focused light. This arrangement illuminates a larger area of the retina more evenly and does not need critical adjustment, but I prefer the focused light because small battery operated bulbs can be used and this eliminates the risk of introducing mains hum from lamp cables. The apparatus is also more compact and can easily be adusted to suit the position of the animal.

Electrodes.—Karpe (1945, 1948) uses contact lenses containing the corneal electrode for his clinical work. I have used lens shells

made from perspex on rabbits. These had the silver wire sealed through the perspex to prevent drainage of saline. One advantage of this electrode over the wick type is that small movements of the animal do not displace it. But in general wick electrodes have been used because so many different sizes of contact glass would be needed to fit different animals. If records are being taken from one animal species only and all animals used are about the same size, contact glass electrodes may be preferable, but for general work wick electrodes of the type described are satisfactory.

Recording device. — Many workers have used ink-writers for recording instead of cathode ray tubes. Ink-writers have both advantages and disadvantages. A permanent record is produced at once; the cost of recording paper is much less than film; the instruments occupy very little space and multiple instruments are available which will produce several records simultaneously on the same paper. The disadvantages are that the movements of the pen must inevitably possess considerable inertia, and even with modern instruments accurate reproduction of frequencies greater than 100 cs./second is not possible. If rapid changes are to be measured, for example the initial rise of the b-wave of the electrotinogram, there is always some over-swing of the pen and arc distortion is also always present. Cathode ray tubes, on the other hand, are, for our purpose without inertia and accurate reproduction of wave forms can be expected from D.C. to very high frequencies. The chief drawback to the cathode ray tube is that it is difficult to observe the wave form and to produce a permanent record simultaneously. This may be achieved by using a single stroke time base coupled to the shutter of the stimulator and exposing one frame at a time with a long persistence tube, but I find it more convenient to dispense with the time base and use continuously moving film with a short persistence tube, even though the exact shape of the wave cannot be seen clearly until the film is developed.

RESULTS

The electroretinograms recorded from normal guinea pigs, rabbits and pigeons confirm the results of other workers. Adrian (1946), using a different machine, showed that the pigeon was far more sensitive to red light than to blue and that the reverse held for the rabbit. My results have confirmed this. It is difficult to reconcile this large response to red light found in the pigeon with Granit's (1947) view that there is a particularly close association between the b-wave and rod activity.

The difference in sensitivity between the rabbit and the pigeon shown by the dark adaptation curves is difficult to explain. From the behaviour of the creatures in their natural environment one

would expect the rabbit's eye to be much more sensitive to dim light. From the response shown by the electroretinogram, however, the reverse would appear to be the case. It seems unlikely that the retina of the rabbit is, in fact, less sensitive than that of the pigeon, it is more probable that the difference lies in the pick-up of potential by the electrodes. The anatomy of the pigeon's is such that a more favourable positioning of the electrodes is possible than with the rabbit. There may also be differences in the conductivity of the tissues and some shunting may take place in the rabbit's eye.

Charpentier (1936) determined the effect of vitamin A deficiency in the rat on its electroretinogram. He measured the curve of dark adaptation in normal and deficient animals by using a constant light stimulus and plotting the height of the b-wave at intervals after a preliminary light adaptation. His results were obtained with a small number of animals but showed that there was probably some reduction in size of b-wave in vitamin A deficiency. His animals did not survive the experiment, so that repeated electroretinograms from the same animal in different stages of the deficiency were unobtainable.

By careful choice of the intensity of the stimulating and adapting light it has been shown (Karpe and Tansley, 1948) that increase in size of the b-wave does correspond to increase in subjective sensitivity during dark adaptation in man.

Another method of plotting the dark adaptation curves of normal and vitamin A deficient rabbits has been used here. After the preliminary light adaptation the minimum stimulus needed to elicit a barely discernible response was measured over a period of 30-60 minutes. This method seems to me theoretically more sound than that used by Charpentier. It is the ultimate limit of sensitivity that we are trying to measure in assessing the dark adaptation curve. By using minimal stimuli there is less risk of light adapting the retina while making the observation and the range of sensitivity is greater.

Dark adaptation curves of rabbits plotted by this method follow the expected course. It is interesting to note that in the vitamin A-deficient rabbits some lowering of retinal sensitivity, judged by the electroretinogram, took place before changes in the eye could be seen with the slit lamp, although the maximum recorded depression of the electroretinogram did not occur until the corneal lesions were well advanced. This is in accordance with human experience where change in dark adaptation occurs well before conjunctival and corneal change (Kitasima, 1939, Yudkin, 1945).

A single dose of vitamin A concentrate containing about 10,000 I.U. was sufficient in some cases to restore the sensitivity to its

original level. Where a doe was fed a deficient diet when the litter was born and the young were continued on the same diet, the dark adaptation curves obtained after the young had been cured by giving vitamin A had to be taken as "normal." Variations from one animal to another made it impossible to decide whether or not a particular curve was indicative of night-blindness without reference to a record taken from the same animal when normal. This variation from animal to animal emphasises the importance of a technique which makes it possible to use a single animal a number of times.

SUMMARY

1. An apparatus and technique for routine electroretinography of experimental animals are described.

2. Examples of animal electroretinograms using this technique are presented.

3. Typical dark adaptation curves of normal rabbit and pigeon obtained by a threshold method are shown.

4. Course of dark adaptation curves plotted during vitamin A deficiency and after cure with vitamin A concentrate are described.

Acknowledgments.—I wish to acknowledge with gratitude the continued interest, guidance and helpful criticism shown by Dr. A. Pirie throughout the whole of this work and also to thank Dr. K. Tansley for reading the manuscript.

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TREATMENT OF INFECTED CORNEAL ULCER BY SUBCONJUNCTIVAL INJECTION OF PENICILLIN IN DOSES OF 1,000,000 UNITS*

BY

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IN earlier communications it has been shown that adequate concentrations of penicillin can be obtained in the cornea and aqueous of the rabbit by subconjunctival injections. It was also shown that by increasing the dose not only is the level of concentration increased but it also persists longer. The addition of vasoconstrictors like adrenalin still further increases both levels and persistence. In the rabbit high aqueous levels persisting for as long as 48 hours could be obtained with a subconjunctival injection of 1,000,000 units crystalline penicillin in 1 ml. of adrenalin (Sorsby and Ungar, 1946, 1948*a*).

The value of subconjunctival injections of penicillin clinically has been recorded in two previous studies. Originally a dose of 50,000 units was used, and to maintain adequate levels these injections had to be given at 6-hourly intervals (Sorsby and Reed, 1947). Subsequently the dose was increased progressively to 500,000 units in one injection at 24-hourly intervals (Sorsby and Ungar, 1948*b*). These large doses were tolerated if white crystalline penicillin was used.

The present study covers 30 consecutive cases of infected corneal ulcer, generally complicated by hypopyon, and treated with doses of 1,000,000 units at either 24-hourly or 48-hourly intervals. Cases of hypopyon iritis were excluded. The series fell into two groups, those in which the eye was previously healthy and those in which it was not. In all cases the diagnosis of infected corneal ulcer was established on the clinical evidence of the ulcer showing either a sloughy base, or sloughy infiltrated margins with or without interstitial infiltration. In 25 cases hypopyon was present, and in all cases bacteriological examination was carried out, generally with positive results.

CASE REPORTS

PREVIOUSLY HEALTHY EYES

(Table A)

Of the 17 cases in this group, 14 responded promptly to penicillin and did well. The 3 patients who did not respond to penicillin

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within 24 hours all showed Gram negative bacilli, and penicillin treatment was replaced by streptomycin.

Penicillin Sensitive Cases

The patients, 11 men and 2 women (Nos. 1-13 in Table A), were of ages ranging from 23 to 66 years. In only one patient was there no history of trauma. In 4 cases corneal foreign bodies had been removed, and in 3 there was a history of a blow on the eye. In the remaining 5 cases the infected ulcer followed respectively on grit, sand, coal dust, tobacco ash and a scratch from a child's nail. One patient had two ulcers, the second being a relapse of the first, 14 days after he took his own, unauthorised, discharge from hospital. He figures twice in the table as 13a and 13b.

Hypopyon was absent in one case, in one it was represented by cells in the anterior chamber, in 8 it was present, though minimal, and in the remaining 4 it filled ¼ of the anterior chamber. Pneumococci were found on smear or culture in 5 cases. In 3 cases no organisms were obtained, and the remainder yielded only staphylococcus albus or B. xerosis.

Number and interval of injections

The initial severity of the condition determined the number of injections the patient received and the intervals at which they were given. The following summary table extracted from Table A brings out the salient features.

It will be seen that only one case required more than 2 injections, and that in most cases the second injection was given after 48 hours.

Response to treatment

All patients showed a clear response to treatment within 24 hours except one patient in whom the infection was not controlled until 72 hours. In the 8 patients who had a minimal hypopyon at the start of treatment, this had become absorbed within 24 hours. Of the 4 patients with hypopyon filling a quarter of the anterior chamber, two took two days and two five days for the hypopyon to disappear. One case was treated as an out-patient; of the others 7 required in-patient treatment for 5 to 9 days, 3 for 10 to 14 days, 1 for 16 days and one discharged himself after two stays of 5 days and 8 days respectively.

End-results

One month after discharge, the visual acuity was 6/5, 6/6 or 6/6 pt. in 5 cases, 6/9 or 6/9 pt. in six cases, and 6/18 in two cases. The cornea was clear in 4 cases, there was a superficial

SUMMARY TABLE I

Showing number of injections in relation to severity of the lesion; previously healthy eyes, penicillin sensitive cases.

State.	No. of cases.	Number of injections.
Infected cornea only without hypopyon.	1	Two injections at 48-hourly intervals.
Infected cornea with cells in anterior chamber.	1	One injection as out-patient.
Infected cornea with minimal hypopyon.	8	Two injections at 48-hourly intervals in 7 patients. One subconjunctival injection on admission followed by a retrobulbar injection 72 hours later in one case.
Infected cornea with hypopyon filling a quarter of the anterior chamber.	4	Two injections at 24-hourly intervals in two patients. Two injections at 48-hourly intervals in one patient (who discharged himself before treatment was complete.) Four injections, two at 24-hourly intervals, followed by two at 48-hourly intervals in one patient.

nebula in 8 cases, and a dense nebula in the remaining case. The results were considered good in all cases. The four most severely affected patients, those who showed hypopyon filling a quarter of the anterior chamber, finally showed vision of 6/9, 6/9, 6/18 and 6/9 respectively. Of the two cases with 6/18 vision, one was an elderly patient of poor intelligence, and the other had a central nebula partially obstructing the pupil. The one case left with a dense corneal scar was the only patient in this series who had had carbolization before penicillin treatment was undertaken.

Penicillin Insensitive Cases

These three ulcers (Nos. 14-16, in Table A) all followed removal of foreign bodies, and in all three Gram negative bacilli were found in the conjunctival sac. In one case, pneumococci were grown as well. Twenty-four hours after the first injection of penicillin, not only was there no response but the ulcers were markedly worse. In all three patients the clinical picture was similar and rather characteristic: a sloughing dirty white, and somewhat heaped up lesion with rapidly spreading and extensive interstitial infiltration. In these cases no attempt was made to persist with penicillin.

Treatment was changed to streptomycin and the results will be recorded in a subsequent study.

SUMMARY TABLE II

End result as to vision a month after discharge of the cases shown in Summary Table I.

State.	No. of cases.	End result	
		Vision with correction where necessary.	No. of cases.
Infected cornea only without hypopyon.	1	6/18 (? better)	1
Infected cornea with cells in anterior chamber.	1	6/9	1
Infected cornea with minimal hypopyon.	8*	6/5	1
		6/6 or 6/6 pt.	4
		6/9 or 6/9 pt.	2
Infected cornea with hypopyon filling a quarter of the anterior chamber.	4	6/9	3
		6/18	1

*In case 13a final vision could not be recorded. The patient figures in the next group with vision of 6/9.

SUMMARY TABLE III

Showing the final condition of the cornea in the cases shown in Summary Table I.

State.	No. of cases.	End-result	
		State of cornea.	No. of cases.
Infected cornea only without hypopyon.	1	Superficial nebula.	1
Infected cornea with cells in anterior chamber.	1	Clear.	1
Infected cornea with minimal hypopyon.	8*	Clear.	3
		Superficial nebula.	3
		Dense scar (peripheral).†	1
Infected cornea with hypopyon filling a quarter of the anterior chamber.	4	Superficial nebula.	4

*Case No. 13a omitted as no end-result could be recorded. The patient figures in the next group as a case with superficial nebula.

†Carbolized before penicillin treatment was undertaken.

TABLE

Previously

No.	Sex	Age	Clinical Condition	History of trauma	Organisms	Hypopyon	Response to penicillin noted within	Treatment other than subconjunctival penicillin and mydriatics
1	M	47	Superficial infiltration of corneal ulcer.	Blow from plant	Staphylococcus Pneumococcus B. Morax-Axenfeld	Minimal	24 hours	Nil
2	M	66	Corneal ulcer with superficial infiltration	Tobacco ash in eye	Staphylococcus Pneumococcus	Nil	72 hours	Nil
3	M	35	Corneal ulcer with superficial infiltration	Foreign body removed	B. Xerosis Staphylococcus albus	Mimimal	24 hours	Carbolized prior to penicillin treatment
4	M	45	Corneal ulcer with superficial infiltration	Foreign body removed	B. Xerosis	Cells in anterior chamber only	24 hours	Nil
5	F	45	Corneal ulcer with much slough and superficial infiltration	Coal dust in eye	Pneumococcus Staphylococcus	¼	24 hours	Nil
6	M	36	Corneal ulcer with superficial infiltration and mild iritis	Blow from piece of concrete	Staphylococcus albus B. Xerosis	Minimal	24 hours	Nil
7	M	45	Corneal abrasion became an ulcer	Piece of grit in eye	Staphylococcus albus Pneumococcus B. Xerosis	Minimal	24 hours	Nil
8	M	34	Corneal ulcer with superficial infiltration	Sand in eye	Nil in smear culture	Minimal	24 hours	Nil
9	F	43	Corneal ulcer with deep infiltration and advancing edge	No trauma	B. Xerosis	¼	24 hours	Nil
10	M	41	Corneal ulcer, deep infiltration	Scratch by child's nail	Nil in smear or culture	Minimal	24 hours	Subconjunctival penicillin 200,000 units 7 injections before seen
11	M	50	Corneal ulcer with superficial infiltration	Foreign body removed (piece of tile)	Staphylococcus albus B. Xerosis	½	24 hours	Nil
12	M	33	Corneal ulcer with superficial infiltration and striate keratitis	Foreign body removed Rust ring scraped	Nil in smear or culture	Minimal	24 hours	Nil
13	M	23	(*a*) Corneal ulcer. sloughing	Struck by piece of clinker	Pneumococcus Gram negative diplobacilli	¼	24 hours	Nil
			(*b*) Corneal ulcer, sloughing	No trauma	Staphylococcus albus	Minimal	24 hours	Nil
14	M	26	Corneal ulcer with interstitial infiltration	Foreign body removed	B. proteus B. subtilis	Nil	Nil within 24 hours	—
15	M	59	Corneal ulcer with interstitial infiltration	Foreign body removed	B. pyocyaneus	Nil		—
16	M	55	Corneal ulcer with localized interstitial infiltration	Foreign body removed	Pneumococcus Gram negative bacilli	Nil		—

A

healthy eyes

Routine subconjunctival penicil.in	Duration of in-patient treatment in days	Duration of hypopyon in days	Visual acuity			Final condition of cornea	Result	Remarks
			On admission	On discharge	After 1 month			
2 injections 48 hour interval	5	1	6/9 pt.	6/9	6/6	Very slight nebula	Good	—
2 injections 48 hour interval	14	—	6/60	6/18	6/18	Faint nebula	Good	Slow response
2 injections 48 hour interval	10	1	6/36	6/12pt.	6/9 pt.	Dense scar (peripheral)	Good	—
1 injection	—	Cells gone in 3 days	6/12	—	6/9	Clear	Good	Treated as out-patient
2 injections 24 hour interval	9	2	Hand movements	6/24	6/9	Central nebula	Good	—
2 injections 48 hour interval	9	1	6/24	6/18	6/6	Faint nebula only	Good	—
2 injections 48 hour interval	5	1	3/60	6/12	6/9	Cornea clear	Good	—
2 injections 48 hour interval	6	1	Counts fingers	6/36	6/6 pt.	Clear	Good	Developed iritis in the other eye six weeks after discharge.
4 injections 2 at 24 and 2 at 48 hour intervals	13	5	Hand movements	2/60	6/9	Large faint superficial nebula	Good	—
2injections 1 subconjunctival on admission, 1 retrobulbar after 3 days	16	1	6/36	6/18	6/5	Nebula	Good	Treated elsewhere with subconjunctival penicillin in doses of 200,000 units; 7 injections before seen.
2 injections 24 hour interval	9	5	Hand movements	6/18	6/18	Faint central nebula	Good	—
2 injections 48 hour interval	5	1	5/60	6/24	6/6 pt.	Clear	Good	—
2 injections 48 hour interval	5	2	Couuts fingers	—	—	—	—	Patient discharged himself before treatment was complete and was readmitted after 14 days with a relapse. He again discharged himself before treatment was complete.
2 injections 48 hour interval	8	1	4/60	6/36	6/9	Nebula	Good	
1 injection	—	—	—	—	—	—	—	No response to penicillin. Gram negative culture. Treatment changed.
1 injection	—	—	—	—	—	—	—	
1 injection	—	—	—	—	—	—	—	

TABLE

Previously injured

No.	Sex	Age	Clinical Condition	History of trauma	Organisms	Hypopyon	Response to penicillin noted within	Treatment other than subconjunctival penicillin and mydriatics
1	M	65	Corneal ulcer 1 month ago. Never settled. Absolute glaucoma.	No trauma	B. Xerosis	½	24 hours	Not known
2	M	63	? Old mustard gas keratitis. 3 previous attacks. Perforating ulcer treated—returned with hypopyon.	'Knocked eye'	B. Morax-Axenfeld	⅓	24 hours	Gutt. zinc sulph. ¼% two hourly
3	M	35	Intraocular foreign body with traumatic cataract two years ago.	Corneal foreign body removed	Staphylococcus	Minimal	24 hours	Nil
4	M	59	Eye red and painful six months. ? previous attack. Corneal ulcer.	No trauma	Staphylococcus albus Pneumococcus	Minimal	72 hours	Carbolized before seen
5	M	50	Dendritic ulcer three years ago—vascularized scar. Corneal ulcer with superficial infiltration.	No trauma	Staphylococcus Pneumococcus	Minimal	24 hours	Tarsorraphy
6	M	55	Ciliary staphyloma—band shaped opacity—staining area.	No corneal sensation	Staphylococcus aureus	Present	48 hours	Lids silvered Carbolization before seen
7	F	67	Lysol burn 18 years ago. Corneal ulcer one year ago. Corneal ulcer with superficial infiltration.	No recent trauma	Staphylococcus albus	½	—	Sulphonamide by mouth
8	M	28	Old interstitial keratitis active. Corneal ulcer.	Injury with wire	Staphylococcus Pneumococcus	Present	72 hours	Penicillin intramuscular 2,000,000 dly.
9	F	55	Central vascular scar from old injury. Corneal ulcer with deep infiltration of old scar like corneal abscess.	—	Nil in smear and culture	⅛	24 hours	Gutt. penicillin
10	F	39	Previous attack ten weeks ago—incompletely cured—relapse Corneal ulcer—interstitial infiltration.	No trauma	B. Xerosis	½	24 hours	Nil
11	F	54	Corneal ulcer. Old phlyctenular scars.	No trauma	Staphylococcus albus Pneumococcus B. Xerosis	Nil	24 hours	Nil
12	F	47	Dendritic ulcer with secondary infection.	—	Staphylococcus Xerosis	½	Nil	—
13	M	67	Previous 'eye trouble', nature unknown, Raised tension, congested eye, corneal abscess.	No trauma	Gram negative bacilli Staphylococcus aureus	Minimal	Nil	—

B

or diseased eyes

Routine subconjunctival penicillin	Duration of in-patient treatment in days	Duration of hypopycn in days	Visual acuity			Final condition of cornea	Result	Remarks
			On admission	On discharge	After 1 month			
2 injections 48 hour interval	5	5	No perception of light	No perception of light	No perception of light	Well healed Nebula	Good	—
3 injections 24 hour interval	12	3-5	—	Counts fingers	Counts fingers	Healed Old scar	Good	—
2 injections 48 hour interval	7	1	Hand movements	Hand movements	Hand movements	Cornea clear	Good	—
3 injections intervals of 3 days and 48 hours	24	8-11	2/60	6/60	6/9	Nebula	Good	—
2 injections 48 hour interval	27	1	Counts fingers	6/24	6/24	Old vascularized scar	Good	—
2 injections 48 hour interval	54	4	No perception of light	No perception of light	No perception of light	Settled	Fair	—
6 injections at intervals of 72, 24 and 48 hours	9	—	Perception of light	—	—	Enucleation Hypopyon responded but relapsed	Bad	—
6 injections 48 hour interval	7	7	Counts fingers	6/18	6/18	Dense circumscribed scar. Interstitial keratitis inactive	Good	—
2 injections 48 hour interval	7	3	Hand movements	—	Hand movements	Healed Vascular scar as before	Good	—
4 injections 48 hour interval	15	8	6/12	6/12	6/12	Faint nebula	Good	—
2 injections 4 day interval	9	—	6/60	—	6/12	Nebula with faint pigmentation	Good	—
1 injection	—	—	—	—	—	—	—	No response to penicillin Treatment changed to streptomycin. ? A case of hypopyon iritis.
1 injection	—	—	—	—	—	—	—	No response to penicillin Treated with streptomycin.

PREVIOUSLY INJURED OR DISEASED EYES

(Table B)

Of the 13 cases in this group, 11 responded satisfactorily to penicillin and 2 did not. Of the 11 who responded to treatment, one patient none the less lost his eye owing to a relapse in a grossly damaged eye (No. 7 in Table B). In one of the two cases without response to penicillin Gram negative bacilli were present in the conjunctival sac, and in the other—a case of dendritic ulcer—staphylococci and B. xerosis were isolated.

Penicillin Sensitive Cases

These 11 patients (Nos. 1-11 in Table B), seven of whom were men, were between the ages of 28 and 67 years. The condition of the eye prior to the onset of the corneal infection was: old corneal ulcer or abscess in 3 cases; chronic or absolute glaucoma in 2 cases, and in 1 case each the following lesions respectively were present: old interstitial keratitis, old lysol burn, phlyctenular scars, dendritic ulcer, old intraocular foreign body, and ? mustard gas keratitis.

Hypopyon was absent in one case only. It was minimal in 3; in 2 cases one-half of the anterior chamber was occupied by the hypopyon; in 1 case each $\frac{1}{3}$, $\frac{1}{4}$, and $\frac{1}{8}$ of the anterior chamber was filled; in two cases hypopyon was recorded as present without further specification. There was a history of recent trauma in 3 cases only. Pneumococci were found in 4 cases, staphylococcus aureus in 1 case, Morax-Axenfeld bacillus in 1 case, and the rest gave only staphylococcus albus or xerosis. In one case, no organisms were seen in the smear or grown in culture, due probably to previous treatment.

Number and interval of injections

As in the uncomplicated cases the initial severity of the condition determined the number of injections the patient received, and the intervals at which they were given. Summary Table IV extracted from Table B brings out the salient features.

It will be noted that in 6 of the 11 cases only 2 injections at intervals of 48 hours or more were given, and in 2 more only 3 injections.

Response to treatment

Most patients showed a clear response to treatment within 24 hours except one in which the hypopyon responded only after 5 days and later relapsed, leading to loss of the eye (No. 7 in Table B). Four patients were in hospital a week or less, 4 more between 1 and 2 weeks, and 3 patients for 3 weeks or more.

SUMMARY TABLE IV

Showing number of injections in relation to severity; initially diseased eyes, penicillin sensitive cases.

State.	No. of cases.	Number of injections with intervals.
Infected cornea with—		
No hypopyon.	1	Two injections at four day intervals.
Minimal hypopyon.	3	Two injections at 48-hourly intervals in two cases. Three injections at intervals of three days, and two days respectively in one case.
Hypopyon filling.		
⅛ of anterior chamber.	1	Two injections at 48-hourly intervals.
¼ of anterior chamber.	1	Two injections at 48-hourly intervals.
1/3 of anterior chamber.	1	Three injections at 24-hourly intervals.
½ of anterior chamber.	2	Six injections at 72-, 24- and 48-hourly intervals in one case. Four injections at 48-hourly intervals in one case.
Hypopyon "present."	2	Two injections at 48 hourly intervals in one case. Six injections at 24-hourly intervals in one case.

End-results

As already noted one patient, after an initial response, relapsed and the eye was enucleated. This was an old lysol burn of 18 years standing with perception of light only and a hypopyon occupying half the anterior chamber at the start of treatment. Two patients had no perception of light before the attack. In the remaining 8 patients, the end result (one month after discharge) was vision of 6/24, 6/18 and 6/12 in one case each; 6/9 in two cases; and C.F. or H.M. in 3 cases, but in these 3 patients visual acuity was the same as before the cornea became infected.

Apart from the eye which came to enucleation, the final condition of the cornea was in no case markedly worse than it originally had been. Having regard to the condition of the eye at the start of treatment, the results were considered to be good in 9 cases, fair in one, and bad in one case.

Penicillin Insensitive Cases

In two cases (Nos. 12 and 13 in Table B) there was no response to penicillin within 24 hours, and the treatment was changed. One case was a dendritic ulcer with secondary infection; staphylococcus and bacillus xerosis were present. It is possible that the hypopyon was of the iritis hypopyon type. In the second case Gram negative bacilli in addition to staphylococcus aureus were present. Both these cases were treated with streptomycin.

Discussion

THE VALUE OF PENICILLIN IN INFECTED CORNEAL ULCERS

The value of penicillin in the treatment of infected corneal ulcers due to penicillin-sensitive organisms is no longer in dispute. It is such that the older methods of treatment, including oral sulphonamide therapy, have now no place in the management of infected corneal ulcers. Heat cauterisation in particular must now be regarded as a superseded barbaric procedure, and carbolization as little better.

What is still at issue is the mode of applying penicillin. Little is to be expected from the instillation of drops—which are rapidly washed out—or from dusting solid crystalline penicillin on to the infected surface—for such penicillin is rapidly dissolved and readily eliminated. Penicillin ointments, however concentrated, do not give such high levels as are obtained by subconjunctival injection. Ionization of penicillin applied by means of a corneal bath presents some technical as well as theoretical difficulties, and there is nothing to suggest that it gives as persistently high levels as are obtained by subconjunctival injections. Subconjunctival injection is therefore the method of choice. The high tolerance of the eye to crystalline penicillin allows the use of massive doses and the present series of cases shows that the subconjunctival injection of doses of 1,000,000 units is possible, clinically as well as experimentally. The advantage of these massive doses lies in the fact that they render unnecessary many injections at frequent intervals. In fact, the milder cases respond to one injection, and a second injection in many of the cases recorded here has been in the nature of a consolidating dose rather than an essential measure in treatment. It is clear that in most cases the second injection need not be given until after 48 hours, though with the present limited experience it is safer to give a second injection after 24 hours in severe cases. It will be seen from Table A, and the corresponding summary table I that of the 14 cases of uncomplicated infected corneal ulcers treated with massive doses of penicillin subconjunctivally, only one patient required more than two

injections. It is likely that in nine patients one injection would have been adequate instead of the two they actually received.

There is nothing to be gained by persisting with the method of treatment by six-hourly injections of 50,000 units as advocated previously. The results in the present series are certainly not inferior to those recorded in the previous study.

There is likewise nothing to be gained by an unnecessary polypharmacy which combines oral sulphonamide with local penicillin therapy. Such measures may be justified in exceptional cases; they are unnecessary as a routine.

TECHNICAL CONSIDERATIONS

A dose of 1,000,000 units crystalline penicillin dissolves without difficulty in 1 ml. of water. It dissolves as readily in an equal quantity of 0·5 ml. water and 0·5 ml. adrenalin 1 : 1,000. If it is desired to replace the water by procaine, it is essential that the penicillin should first be dissolved in the adrenalin and an additional 0·25 ml. of water, for penicillin in procaine solution forms a cloudy suspension from which the penicillin tends to crystallise out. Saline should not be used as such solutions of penicillin are markedly hypertonic. If severe iritis is present rapid mydriasis may be obtained by incorporating mydricaine in the solvent. In this case the solvent used should be mydricain min. v, adrenalin 1 : 1,000 min. v, aq. dist. ad. 1 ml. Alternatively the penicillin can be dissolved in 5 minims of adrenalin 1 : 1,000 to which is added 10 minims of a stock solution of water containing atropine sulphate 1/40 grain and cocaine hydrochlor. $\frac{1}{8}$ grain.

It is advisable to test the sensitivity of the patient to adrenalin before using it in a subconjunctival injection. If a subcutaneous injection of 2 minims of adrenalin 1 : 1,000 gives no unpleasant reaction within 15 minutes, it may be assumed that no harm will result from the full injection. No general reactions were observed in the present series.

No sign of corneal reaction was observed after any of these injections. Chemosis is inevitable and is occasionally accompanied by some subconjunctival haemorrhage, especially in a congested eye. It clears up completely, though occasionally not for a few weeks.

Pain after the injection is usually slight, lasting only for a few minutes, or half an hour at the most. Occasionally patients complain of more severe discomfort. If care is taken to inject beneath the laxest part of the conjunctiva, this can be reduced to a minimum and is usually easily controlled with analgesics. It is doubtful whether the use of procaine as the solvent does anything to

reduce the discomfort, which is probably caused by the hypertonicity of the injection.

No general reaction from the massive dose of penicillin was observed.

SUGGESTED SCHEME OF TREATMENT

Once the diagnosis of infected corneal ulcer has been made the object must be to obtain immediate control of the penicillin-sensitive organisms and the earliest possible knowledge of the insensitive ones. To this end the following scheme is suggested.

Immediately on admission

A smear and culture from the conjunctival sac should be taken and an adrenalin sensitivity test carried out. If the use of adrenalin is not contra-indicated, the patient should be given a subconjunctival injection of 1,000,000 units of crystalline penicillin in mydricain, m.v, adrenalin 1 : 1,000 m.v, and aq. dist. ad. 1 ml. (or alternatively 1,000,000 units dissolved in 5 minims of adrenalin 1 : 1,000 and 10 minims of a stock solution of water containing atropine 1/40 grain and cocaine $\frac{1}{8}$ grain). On no account must any but white crystalline penicillin be used.

During the first 24 hours

No treatment is needed beyond keeping the eye bandaged and instilling atropine to maintain mydriasis.

Twenty-four hours after admission

If the condition shows marked improvement a further injection should not be needed until 48 hours after the first, but in severe infections it may be wise to give the second injection at 24 hours. For the present it is perhaps best to maintain 24-hourly injections as long as any hypopyon is present. If, after 3 or 4 injections, it proves difficult to continue with subconjunctival injections, the retrobulbar route may be used. If there is no substantial improvement the possibility of an insensitive organism must be considered, whilst deterioration indicates that the infection is almost certainly due to a penicillin-insensitive organism, and some other form of treatment such as streptomycin therapy should be instituted.

Forty-eight hours after admission

If, after a second injection at 24 hours, the condition is inadequately controlled, the infection should be regarded as due to a penicillin-insensitive or relatively resistant organism and treatment changed.

The bacteriological findings may confirm the clinical diagnosis at any stage. More weight, however, should be attached to clinical course than to bacteriological findings.

Summary

(1) A series of thirty consecutive cases of infected corneal ulcer treated by subconjunctival injections of 1,000,000 units penicillin is recorded. In 17 cases the eye had been healthy previous to the onset of the infected corneal ulcer. In 13 cases a corneal infection occurred in eyes previously diseased.

(2) Of the 17 cases in the first group, 14 responded promptly to penicillin treatment. The three patients who did not respond to penicillin were cases of infected corneal ulcer due to Gram negative bacilli, insensitive to penicillin. The 14 cases (13 patients) with good response showed a varying amount of hypopyon reaction. All but one of these cases required not more than two subconjuctival injections of penicillin. It is likely that in most cases one injection would have been adequate. The end-result as to vision was 6/9 to 6/5 in 11 patients.

(3) The 13 cases of infected corneal ulcer in previously diseased eyes contained two that failed to respond. Of the remaining 11 cases, one eye—an old-standing chemical burn—ended in enucleation; the result of treatment could be considered as satisfactory in 9 cases, and only fair in one.

(4) Treatment of infected corneal ulcer by subconjunctival injections of 1,000,000 units of penicillin has the advantage of bringing the condition under control within 24 hours in most cases. Frequent injections are unnecessary, recovery is rapid, corneal scarring minimal and the visual results gratifying.

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AUREOMYCIN IN OPHTHALMOLOGY

(A Preliminary Report)

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AUREOMYCIN (Lederle), a new antibiotic which has been obtained from a mould belonging to the streptomyces group, has not been employed sufficiently in ophthalmology to allow an accurate assessment of its value. The fact, however, that it has been shown to inhibit the growth of a considerable number of organisms such as staphylococcus, pneumococcus and H. influenzae, as well as of rickettsiae and a number of viruses, indicates that it may perhaps occupy a valuable place in our therapeutic armamentarium. One important use, of course, is in the treatment of organisms which are insensitive to penicillin. It is extremely suggestive that it has been found to be effective against the group of large-sized viruses typified in those responsible for lymphogranuloma venereum and psittacosis.

The only reports of a large group of infections treated by aureomycin in the literature, are those of Braley and Saunders (1948-1949). These authors treated a number of various conditions, finding the drug to be effective against several gram-positive cocci and gram-negative bacilli; they also found it to be an effective therapeutic agent in inclusion conjunctivitis and in herpes simplex of the cornea. While being unable to reach a definite conclusion, they found it more effective against the virus of epidemic keratoconjunctivitis than any other antibiotics or drugs which have yet been tried. It is interesting that they treated with success one case of trachoma. A second report on the treatment of trachoma has come from Portugal (Moutinho, Grilo and Moura, 1949). These authors, using both drops and an ointment given two-hourly day and night for a period of from 2-6 days, reported extraordinarily encouraging results in 15 cases of trachoma at various stages of the disease, many of them showing well developed follicles, cicatrization or ulcerative pannus. They claimed that for the first time a remedy had been found which causes the disappearance of the lesions in a matter of days.

The supplies of aureomycin available to us were small, so that the number of cases reported here are insufficient to allow any firm conclusions. It is interesting that with regard to the various infections found commonly in Great Britain reported in the first part of this paper, the results have not been extremely dramatic; the

control of a virulent case of recurrent hypopyon uveitis, however, is of interest. A small quantity of the drug was sent to Uganda, in view of the fact that trachoma of a virulent type is exceedingly common in this country, and the dramatic results reported may be of great importance. To reason from 8 cases, of course, is extremely dangerous, and before any conclusion can be reached much larger numbers will require to be treated, preferably in different parts of the world; but if the promise of these early cases is maintained, a therapeutic agent will have been discovered which may bring great changes, socially and economically, to vast tracts of the world.

SOME CASES TREATED WITH AUREOMYCIN

BY

D. AINSLIE

ALTHOUGH the number of cases treated here with aureomycin is still too small to enable any definite conclusions to be drawn, I think it may be of value to record the results obtained so far. Reports of 33 cases are given and these consist of inflammatory diseases of uncertain aetiology, those due, or believed to be due to viruses and those due to organisms insensitive to penicillin. Many staphylococci, streptococci and pneumococci are highly sensitive to aureomycin, but simple infections with the organisms have not been treated as they also respond readily to penicillin.

Administration

For systemic use the drug was administered orally in the form of aureomycin hydrochloride in doses (for adults) from 500-750 mgms. six-hourly up to a total of approximately 20 gms.

The HCl salt is too irritating to be instilled into the conjunctival sac and consequently aureomycin borate must be used for local application. In every case the drops consisted of:

Aureomycin HCl	25 mgm.
Sodium borate	25 mgm.
Sodium chloride	625 mgm.
Distilled water	5 cc.

One or two drops of this solution were instilled hourly or two-hourly.

After the water has been added to the mixture, the aureomycin

rapidly loses its antibiotic activity and therefore fresh drops must be prepared at least every 48 hours.

Cases requiring local administration only were treated as out-patients except where there was reason to believe that the drops were not being properly instilled. With the exception of three cases, all who had the drug systemically were admitted to hospital.

Toxic Manifestations

No serious toxic effects were noticed. Of the eighteen cases receiving aureomycin orally twelve had mild diarrhoea and of these nine complained of nausea; vomiting occurring in three. The administration of Aludrox gm. 2 following the dose of aureomycin reduced the nausea in some cases only. One patient complained of no symptoms until, after receiving 18 gm., she had a syncopal attack. The drug was stopped and she improved rapidly. It is difficult to say whether or not the attack was caused by the aureomycin.

Cases Treated

Blepharitis (one case). This patient had had blepharo-conjunctivitis for six months. This was associated with recurrent styes, thirteen having occurred. The eyes were constantly red and sore. Previous treatment had consisted of three courses of intramuscular penicillin, the total dosage being about 7 million units. There had been several courses of penicillin drops. Intra-muscular collosol manganese had also been given. When seen on October 13, 1949, she had marked blepharitis with minimal conjunctivitis. A culture had been taken and had shown a staphylococcus pyogenes which was insensitive to penicillin but sensitive *in vitro* to aureomycin.

Treatment with aureomycin was started, giving 750 mgms. six-hourly up to a total of .18 gms. In addition, drops were instilled hourly. At the end of a week the eyes felt comfortable and appeared much improved. When seen again on November 13, 1949, the left eye appeared normal, but there was slight conjunctivitis of the right. Further drops were given for four days. On November 27, 1949, both eyes appeared normal. It is impossible to say that the condition will not recur, but it certainly appears that aureomycin has been of great value.

Conjunctivitis due to H. influenzae (*one case*)

This patient was a child aged 2¼ years who had had discharging eyes and nose for nine months. Penicillin drops, albucid and mercury oxycyanide lotion had failed to bring any improvement. On May 16, 1949, aureomycin drops were instilled into each eye and to each nostril every hour and continued for four days. At the end of this time the eyes and nose were dry for the first time in nine months. Treatment was stopped, but three days later the symptoms recurred. On May 25, 1949, treatment with further drops was started and also 250 mgm. of aureomycin was given six-hourly by mouth to a total of 5,500 mgm. The lacrimal sacs were syringed daily with aureomycin. On June 1, 1949, the eyes began to discharge slightly. The condition remained static until June 23, 1949. A further culture on this date revealed *H. influenzae* and culture from the eyes and noses of the parents also revealed the same organism, though the parents were symptom-free. It was thought desirable to treat all three subjects, as there was the possibility of re-infection. This was suggested but, unfortunately, the patients did not attend again and it has been impossible to get them to do so.

Although the child was certainly not cured aureomycin was the only drug that had affected his condition favourably.

Inclusion conjunctivitis (one case)

This patient had complained of pricking eyes for seven months. Penicillin and albucid drops had been ineffective. When seen on June 22, 1949, both upper tarsal conjunctivae were injected and covered with minute follicles so small as to give a velvety appearance. Scrapings from the tarsal conjunctivae showed numerous inclusion bodies; there was no growth on culture. Aureomycin drops were applied half-hourly to the everted lids and the lacrimal sacs were syringed with aureomycin daily. Improvement of symptoms and signs occurred. On July 21, 1949, the eyes were slightly red and a further scraping of the conjunctiva showed a few inclusion bodies. Further drops were given and also 12 gm. of aureomycin *per os*. On August 11, 1949, the eyes appeared normal and scrapings revealed no inclusion bodies. The patient has been seen from time to time since, and, though much better, still has a sensation of grittiness. Further scrapings have not revealed inclusion bodies. Although there are now no follicles of the tarsal conjunctivae these remain slightly injected and additional aureomycin has failed to improve this.

Dendritic ulcer (nine cases)

Seven cases of fresh dendritic ulcers were treated with aureomycin drops. In none was there any improvement. One longstanding case with deep corneal ulceration failed to respond to aureomycin drops and a systematic course was equally ineffective. One case which had been carbolized two days previously was treated. The ulcer no longer had a dendritic form, but there was a large, deep ulcer in the lower cornea. Aureomycin drops were given and the ulcer healed after five days. I feel that in this case aureomycin was useful only in so far as it prevented secondary infection.

Herpes ophthalmicus (one case)

This was a case of ophthalmic herpes with iridocyclitis. 15 gm. of aureomycin was given without noticeable effect.

Superficial punctate keratitis (five cases)

All cases were characterized by numerous small points of superficial keratitis, the majority of which involved the epithelial surface and led to staining with fluorescein. In every instance treatment with aureomycin drops was continued for at least seven days, but, apart from temporary subjective improvement in two cases, the conditions were unaffected.

Disciform keratitis (two cases)

The first case, which followed a corneal abrasion, had been receiving treatment with albucid and atropine drops for two weeks before aureomycin was started. The condition was remaining approximately static. Slight improvement occurred during this period.

The second case followed superficial punctate keratitis. On August 22, 1949, keratitis disciformis was diagnosed. Treatment with mydriatics, guttae penicillin and sulphathiazole ionization were tried, but by October 10, 1949, the condition was not improved. On this date there was a dense central corneal opacity, the cornea was thickened centrally and there was marked ciliary injection. Lacrimation was extreme. Aureomycin drops were given hourly for ten days and at the end of this time there was marked improvement, there being only slight ciliary injection and lacrimation. The corneal opacity appeared unchanged.

Iridocyclitis (twelve cases)

In eleven cases the iridocyclitis was chronic and characterized by numerous fine keratic precipitates and circulating cells in the anterior chamber. In every case

the condition was bilateral. In addition two cases showed periphlebitis retinae and in one there was a patch of acute choroiditis. No general disease was found in any of these cases. All patients were treated with aureomycin given orally, the total dosage ranging from 15 to 20 gm. In no case could any definite improvement be observed.

One case of recurrent hypopyon uveitis was treated. The history was of attacks of misty vision and redness of the eyes for nine years until, in 1948, the left vision "went altogether" and the right became permanently much worse than previously. When seen on August 17, 1948, the left eye was quiet with old k.p. and lens opacities, the visual acuity being bare perception of light. The right eye was injected and there was a 1·5 mm. hypopyon and numerous circulating cells in the anterior chamber. The pupil was dilated from previous atropine. Vision was reduced to counting fingers at one metre. Systemic aureomycin was given to a total of 20 gm. On August 24, 1949, the hypopyon had gone and the eye was white, but an aqueous flare remained. The patient continued to be well until October 20, 1949, when the hypopyon again recurred in the right eye. A further 23 gm. of aureomycin was given. On October 27, 1949, the eye was again white and the anterior chamber was clear, except for a few circulating cells. Vision was 3/60. The patient is convinced that the aureomycin has cut short his acute attack in each case. It is, however, uncertain as yet whether it has really influenced the disease favourably.

Sympathetic ophthalmitis (one case)

The case was one of sympathetic ophthalmitis occurring two months after cataract extraction. Systemic penicillin and N.A.B. had been given without success. Aureomycin was given orally, but only up to 7,500 mgms., as the patient, who was already mentally unstable, became unmanageable and the course had to be stopped. No improvement was noticed.

SUMMARY

1. Results obtained in 33 cases treated with aureomycin are given and the method of administration described.

2. Cases of chronic iridocyclitis did not appear to benefit with the possible exception of a case of recurrent hypopyon uveitis.

3. Dendritic ulcers and superficial punctate keratitis did not respond. One case of keratitis disciformis appeared to benefit.

4. A case of blepharitis due to non-penicillin-sensitive staphylococcus has benefited initially.

5. An infection with *H. influenzae* improved while under treatment.

6. An example of inclusion conjunctivitis was treated and showed marked improvement.

7. One case of herpes ophthalmicus and one case of sympathetic ophthalmia were treated without benefit.

I wish to thank the Surgeons of Moorfields, Westminster and Central Eye Hospital and St. George's Hospital for their kindness in referring cases for treatment.

AUREOMYCIN IN TRACHOMA

BY

A. J. BOASE

UGANDA

THROUGH the kindness of Sir Stewart Duke-Elder I have been able to put to a clinical trial the new antibiotic aureomycin (Lederle) in a few cases of trachoma. The number is very small, as was the quantity of aureomycin at my disposal. Nevertheless I feel that a description of the cases and the results obtained will be of interest to others working on the problem of trachoma.

CASE 1. Ganda woman, age 30 years. Profuse lacrimation and photophobia for over a month. There were numerous follicles scattered over the tarsi, and very many of MacCallan's "bleb-like excrescences" chiefly at the transition folds. An early papillary hypertrophy was present. Pannus was obvious to the unaided eye, the vessels reaching to the centre of the corneae. There was nothing to choose between the two eyes.

She was put on 3-hourly aureomycin drops for ten days, after which no treatment of any sort was given. On the 15th day a careful slit-lamp examination was made. I could detect no follicles. The tarsal surfaces which now appeared normal to the naked eye showed a slight roughness under the microscope. Indefinite "sago grains" still seemed to be present in the lower fornices. The most surprising finding was in regard to the pannus: the corneae were bright and had a normal window reflex, and with the slit-lamp all that I could see was the merest fringe of vessels at the upper limbus.

Through an oversight a conjunctival scraping was not taken until the third day of treatment: inclusion bodies were not found.

The patient refused to stay any longer in hospital, insisting that she was cured, and as she has not returned since discharge (August 8, 1949) it might be assumed that there has been no relapse.

CASE 2. An elderly Ganda woman was admitted with acute muco-purulent conjunctivitis superimposed on a trachoma which was otherwise similar to Case 1 though more advanced. She had drops of penicillin and sulphacetamide for three days before being put on aureomycin. The subjective symptoms of the conjunctivitis were considerably relieved by that treatment, but the objective signs of the trachoma were uninfluenced. As in the first case, aureomycin was used in 3-hourly drops. After a few days there was a remarkable improvement in her condition as seen with the unaided eye. Unfortunately she decamped from hospital before I could make a slit-lamp examination, having told the nurse that she saw no sense in staying as she was cured. (The absconding of interesting cases in the middle of a piece of research is something that those working in native hospitals have to contend with.)

CASE 3.—Ganda male, about 40 years old. Eyes bad for two months: profuse lacrimation, distressful photophobia, much mucoid discharge. Gross shaggy papillary hypertrophy interspersed with large blebs which in the fornices stood out in the classical manner of boiled sago or frog's eggs. Pannus vessels large and well below centre of corneae. The right tarsus showed a large splotch of melanin-like pigment from top to bottom and about one third its width. Altogether a typical "bad" trachoma as we see the disease in Uganda with a correspondingly bad prognosis. Conjunctival scraping was unsatisfactory because of haemorrhage from the papillae at the lightest touch: inclusion bodies were not identified.

Patient was put on one drop of aureomycin at 4-hourly intervals. Discomfort soon disappeared and the secretion stopped. On the 10th day I noted that his appearance was normal and that he would not be picked out as a likely trachoma in a parade. He himself said he was cured. The right tarsus still showed obvious

papillae and there was no change in the pigmented patch; in the left tarsus regression of the papillae was more evident. Pannus was now represented by a very narrow fringe of vessels across the limbus. Patient was persuaded that his relief might be only temporary and that an operation would ensure a permanent cure. He readily agreed and a bilateral tarsectomy was performed ten days after stopping aureomycin treatment. The excised tarsi were sent to Sir Stewart Duke-Elder, who has since kindly informed me that "there is no doubt whatever that the slide you sent us is trachoma."

CASE 4. Toro girl, age 15 years. Admitted because of a severe trachoma in her only seeing eye. This, the left, showed gross papillary hypertrophy and macro-pannus over the upper fifth or quarter of the cornea. Photophobia and mucoid secretion were pronounced. The right cornea was opaque and the bulb phthisical, the tarsus similar to the left. There was a marked improvement in the subjective symptoms after a week's treatment with aureomycin one drop at 4-hourly intervals but not as dramatic as in the foregoing cases. It was thought that vernal catarrh might be a complicating factor as the papillae showed a tendency towards cobbling, so the tarsi were excised. The histopathology of the section is that of trachoma and does not suggest vernal catarrh. Noteworthy is the fact that the cellular infiltration is nowhere as dense as one would expect to find in a case of trachoma with similar clinical signs: follicles are conspicuously absent. An unusually high proportion of the deeply-invading epithelial cells show gross distension of the goblet-cell type. I have not recognized any inclusions in the sections.

CASE 5. Ganda male, age about 40 years. Eyes bad for nearly two years. In February, 1949, he was in hospital for two weeks with a trachomatous ulcer in the left cornea. His record shows that there was then gross papillary hypertrophy and marked macro-pannus in each eye. On September 6, 1949, he was readmitted with a very inflamed right eye, the lids being swollen and lacrimation profuse. There was a large trachomatous ulcer just above the centre of the cornea. Each eye showed gross shaggy papillary hypertrophy, and pannus was obvious to below the corneal centre without optical aid. He was put on aureomycin one drop 4-hourly for ten days, during which period he had an acute attack of bacillary dysentery and was treated with a four days' course of sulphaguanidine. On September 19 he insisted on his discharge saying he was cured. A careful examination was made and the following notes recorded. The left tarsus is smooth, shiny and shows fine criss-cross scarring; the right is smooth with just a trace of roughness and shows rather pronounced band-form scarring. Pannus in the left eye is represented by very attenuated vessels in the upper quarter of fifth of the cornea; in the right there are more vessels leading to the healed ulcer but all are thin and regressing. Each cornea shows in the horizontal central area a brown pigmentary stippling in the epithelium (a common finding in trachoma as seen in Uganda).

CASE 6. Ganda male, age about 45 years. Three weeks' history of sore eyes. There was a very fine papillary hypertrophy and many follicles scattered over the upper tarsi with numerous blebs at the transition folds. Macro-pannus was obvious in the upper third of each cornea. The centre of the left cornea was occupied by a large leucoma which extended nearly to the lower limbus. The usual subjective symptoms of photophobia and lacrimation were marked. He was treated with aureomycin, one drop at 4-hourly intervals, for ten days when I recorded that although the fine papillary hypertrophy was still present his condition was vastly different from what it was on admission. He left hospital and was not seen again for six weeks. My notes then recorded that the tarsi appeared perfectly normal and that all that remained of the pannus were a few empty vessels across the limbus. Corrected vision in the right eye was 6/6.

CASE 7. An elderly European lady had had sore eyes for nearly a month, and had been bathing them with boric lotion. Lacrimation was marked in the right eye, less in the left. Numerous follicles were present on the upper tarsi, more so in the right. The slit-lamp showed profuse vascular "bouquets" rising towards the canthi into small papillae. There was no pannus but the upper limbal vessels were full and gave the impression that it would not be long before they started budding. My diagnosis was trachoma, stage 1, but pending pathological

confirmation she was given penicillin drops. The report on a conjunctival scraping was "a very adequate scraping. Purple-staining granules are present in many of the epithelial cells. I am not, however, prepared to say that this undoubtedly trachoma." (A. B. Raper.) Patient returned two days later and said that if anything she thought she was worse; there was certainly no objective amelioration. She was given a 5 mil. bottle of aureomycin and told to put a drop in each eye every three hours. Four days later she reported that she felt a different woman and was certain she was cured. But while the distressing lacrimation had entirely ceased, I was not satisfied that there was any real change in the appearance of the tarsi, so I instructed her to carry on with the drops for another week. When she returned at the end of this period the tarsi appeared normal to the naked eye, although with the slit-lamp a few small follicles and capillary trees could still be identified. She was told to return if the symptoms recurred, however slightly. This was over three months ago, and as she lives quite near me it may be taken that there has been no relapse.

CASE 8. A senior European official had had a sore left eye for over a week. There was no real pain but the discomfort and incessant watering were "getting him down," to use his own words. On the advice of his medical officer he had been using drops of albucid and of penicillin without any benefit, in fact he thought he was getting worse. Like many others who have spent years in the open in tropical countries he has a chronic catarrh of the conjunctiva. On examination I found the left tarsus red and velvety. With the slit-lamp very small follicles could be identified; there was a suspicion of neo-vascularization at the upper limbus. There was no secretion apart from the lacrimation. Conjunctival scraping was inconclusive. He was put on aureomycin 2 drops at 3-hourly intervals for eight days. By then all his symptoms had gone; as a matter of fact he had said he was cured after the third day. Treatment was finished off with an ionisation with zinc sulphate, since when (over three months) he has had no further trouble. In this case the diagnosis of trachoma, stage 1, was made on the slenderest of grounds, and I would not cavil with anyone who declines to accept it. Nevertheless the treatment was based on the diagnosis and the outcome is what was desired.

SUMMARY

Eight cases of trachoma are presented. All were treated with the conjunctival instillation of drops of aureomycin. The therapeutic results, even although the series is much too small to warrant a final conclusion, warrant the opinion that aureomycin will cure the disease in an incredibly short time. The optimum dosage and mode of administration is not yet settled, but in these cases highly satisfactory results followed the simple (and economical) routine of one drop at four-hourly intervals.

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INJECTION OF THE RETINAL VASCULAR SYSTEM IN THE ENUCLEATED EYE IN DIABETIC RETINOPATHY*

BY

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IN the course of our studies in diabetic retinopathy, a preliminary report of which was recently issued in this Journal (Ashton, 1949), many methods of demonstrating the retinal vasculature have been tried, among which injection of the retinal capillaries in the excised eye with a variety of dyes and plastic materials has been attempted and is still being investigated. So far the use of Indian Ink has been found extremely effective and during the course of our work Michaelson and Steedman (1949) published a similar method for injecting the freshly enucleated eye and they have indicated the potentialities of this technique in anatomical and pathological studies. It is thought, therefore, that the publication of photographs of the injected retina from a case of advanced diabetic retinopathy would be of timely interest. Our method varies in detail from that of Michaelson and Steedman.

METHOD

The technique may be applied to either fresh or *post mortem* material. In order to prevent the fixation of blood in the capillaries the whole eye was not placed in formol saline as advocated by Michaelson and Steedman. The free end of the optic nerve is dipped in 10 per cent. formol saline for a few minutes and is then cut transversely with a sharp scalpel to give a clean flat surface. The globe is held inverted in an iris diaphragm and placed under a stereoscopic dissecting microscope. The cut surface of the nerve is illuminated with a point source of light and the pouting central vessels may be clearly seen in the majority of cases. A fine glass capillary canula, bent at an angle of about 120°, is drawn from a glass tube of 5 mm. internal bore and 3½—4 in. in length. The capillary canula, bent at an angle of about 120°, is drawn from a and cut to approximate to the required size. The canula is now attached to the suction tap of an electric pump (Edward's Rotary Vacuum Pump and Compressor) and distilled water is sucked into the tube which holds about 2 ccs. This method of filling

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ensures that no particles enter the tube and block the capillary at the time of injection. The canula is now attached to the pressure tap of the same pump, adjusted to give a pressure of about 10 lbs. and the capillary tube is inserted into the vein or artery. An assistant works the motor switch, thus the operator has only to hold the canula in position. The irrigation of vessels with water lyses the red cells and opens up channels which might otherwise remain blocked. The water is allowed to remain in the vessels for 5-10 minutes for maximum haemolysation to take place and then more distilled water is run through. The vessels are then irrigated with 10 per cent. formol saline to fix them in the distended position. The canula is now charged with Indian Ink as above, and the final injection made. The injected eye is placed in 10 per cent. formol saline for 12 hours. The retina is then removed and mounted in a glass sphere, as described in our preliminary report, except that the optic nerve head is now included with the retina by cutting posteriorly with a sharp spoon, and examined under the microscope and photographed for record purposes.

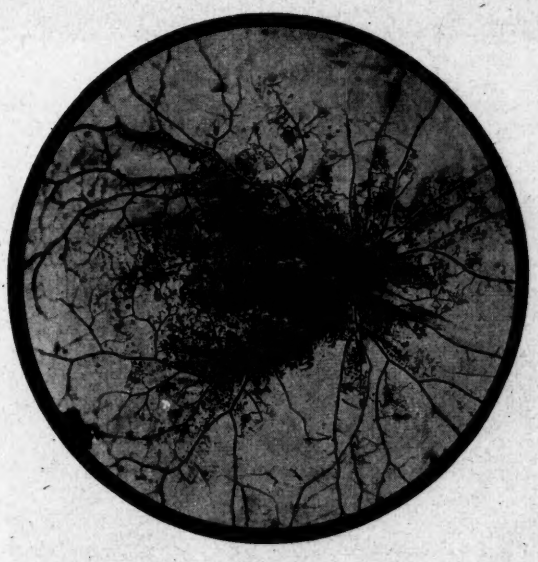

FIG. 1.

Left retina mounted in a glass sphere after injection of the vessels with Indian ink. Shows a Stage III diabetic retinopathy. Scattered haemorrhages and many thousands of micro-aneurysms can be seen. ×4·5.

FIG. 2.

Higher magnification of retina shown in Fig. 1. Note the large number of aneurysms. ×27·5.

FIG. 3.

Injected retina showing many aneurysms, beading, looping and irregularity of the capillaries. ×200.

The case here shown is the retina from an injected right eye taken at *post mortem* from a female aged 71 who had suffered from diabetes for twenty-six years. There is a Stage III diabetic retinopathy with micro-aneurysms, irregular haemorrhages, macular and punctate exudates. Although the injection is not as complete as we have obtained in freshly excised eyes, it is satisfactory for a *post mortem* specimen and the picture clearly shows some thousands of micro-aneurysms. Beading, localised dilatations and looping of the vessels and multiple haemorrhages can be seen. It is believed that it has not previously been realised how surprisingly numerous micro-aneurysms are and the picture is a depressing one for one wonders how it can ever be possible to reverse such a gross and widespread process by the administration of drugs or the control of diet. At best we can only hope to prevent the development of such lesions or, once the condition is established, to attempt to control the haemorrhages.

I am indebted to Dr. Peter Hansell for the photographs.

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CONVERGENCE DEFICIENCY*

An investigation into the results of treatment

BY

A. MELLICK

GLASGOW

OVER the period of twelve months which covered the present investigation, 88 patients attending the out-patient department of the Glasgow Eye Infirmary manifested the subjective and objective features of convergence deficiency. Their ages ranged from 14 to 50 years, 32 being below 20 years of age, 37 in the third decade, 15 in the fourth decade, and 4 in the fifth decade. Of the 88 patients, 51 were females, and 37 males. Thirty-seven cases were emmetropic; in 43 hypermetropia or hypermetropic astigmatism was present, and in 8 myopia or myopic astigmatism.

Fifteen of the 88 cases were considered unsuitable for orthoptic treatment. Of these, 12 suffered from so pronounced a degree of neurosis, that the immediate consideration was the treatment of

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the functional nervous disorder, and in their cases the convergence deficiency was obviously relatively unimportant. Indeed, 6 of the 12 were already receiving psychotherapy; the remaining 6 were referred for similar treatment. Three further cases were deemed unsuitable; two suffered from a post-concussional syndrome of recent origin, and one had sustained a recent subarachnoid haemorrhage. Seventy-three cases, remained, but this number was further reduced since 10 failed to attend or defaulted before the completion of treatment.

An analysis of these ten cases presents features of interest. Three attended on several occasions, and made rapid progress; perhaps with the relief of subjective symptoms they considered that further treatment was unnecessary. In the remaining 7 a marked anxiety state existed. It is not a difficult matter to segregate those individuals who are unlikely to persist with treatment, and much of the orthoptist's time may be saved by judicious selection.

Sixty-three cases completed treatment. This series may be divided into two groups, depending on the association of the neurotic state with the convergence deficiency. There were 48 neurotic subjects, an incidence of 76 per cent. Of the residual 15, in 6 the symptoms had first appeared shortly after an acute illness or debilitating malady, while in the other 9 no apparent precipitating factor was evident.

Thirty-seven patients of the neurotic group were considered to be cured as the result of treatment; four were improved, and seven made no progress. All the 6 cases whose convergence defect succeeded an acute illness or debilitating condition responded to treatment. Of the remaining 9 cases of unknown etiology, 5 were relieved entirely of their symptoms, 3 improved, and 1 proved resistant to treatment.

There is no great discrepancy in the percentage of cures and failures between the two groups. Any true estimation of " cure " must take cognisance of possible relapse—an occurrence which is well recognised—and accordingly relief of symptoms alone can form a true working basis only if the patient is observed over a sufficiently long period. How long the latter should be is difficult to assess. In the present investigation an obvious shortcoming is the inadequacy of follow-up, and the term " cure " must here refer to the immediate relief of symptoms. It should be emphasised, however, that such relief was always attended in this investigation by objective signs of improved convergence power. The converse did not hold true, since it was found that in some of the failures, objective improvement, even up to the full standard of " cure," occurred without corresponding improvement in the symptoms.

It is noteworthy that all 6 cases in which the symptoms developed after an illness were cured. Obviously the prognosis in these cases is excellent, provided one can exclude psychological complications.

Symptomless Convergence Deficiency.—The amount of convergence normally employed in ordinary reading is 21 prism dioptres. Individuals who are capable only of this degree of adduction are employing their maximum convergence continuously while reading or performing equivalent work at near. For comfort, a wider range than this is required, but apparently there exists a group of people with even less than this minimum, who do not complain of symptoms referable to their defective convergence. Among them are to be found workers who, in the course of their occupation, require close application of the eyes for long periods throughout the day.

The number of people in this group, *i.e.*, having less than 21 dioptres of convergence, was 18, and of these, 9 were males and 9 females. Five were engaged in close work, such as clerking, scientific instrument making, etc.; 15 had hypermetropia or hypermetropic astigmatism, and 3 myopia or myopic astigmatism. Their age distribution is shown in the following table.

Age in yrs.	0-20	21-30	31-40	41-50	51-60	61+
No.	4	4	3	5	1	1

In no case was the degree of convergence less than 14 dioptres, and only those showing less than 21 dioptres of convergence have been included. The explanation for the absence of symptoms in this group is not as yet evident.

Symptoms of Convergence Deficiency in the absence of Objective Signs.

There were 29 patients in this group. In all cases, the refraction had been corrected, the phorias were within normal limits, and the duction power was easily sufficient to allow them to carry on their daily work. Nevertheless, all complained bitterly of those symptoms which are typically associated with conververgence deficiency. Their ages ranged from 15 to 56 years. The age distribution is shown in the following table.

Age in years	0-20	21-30	31-40	41-50	51-60
No.	7	17	4	0	1

A study of the refractive state of this group revealed that 12 were emmetropic, 12 had hypermetropia or hypermetropic astigmatism, and 5 had myopia or myopic astigmatism. 14 of the cases were engaged in close work.

Associated Conditions.—Two patients showed evidence of rheumatic heart disease, one suffered from sinusitis and asthma, and in one the symptoms had first appeared following an attack of asthma. Twenty-two patients demonstrated the features of established nervous disorder of the category of anxiety neurosis. Three of the latter patients had previously suffered a nervous breakdown; 11 were receiving treatment from their doctor, or had recently been under medical treatment for " nerves "; while the remaining 8 presented symptoms which are associated with functional nervous disorder. In 3 cases there was no obvious cause for the ocular symptoms.

Functional nervous disorder has been recognised for many years as a basis of symptoms simulating convergence deficiency (Mann). The high incidence in the present series—76 per cent. —suggests that it is by far the commonest etiological factor in this group. The question of why the neurotic subject should fix upon the ocular system for his psychosomatic manifestations remains to be answered; in future investigations of this aspect, the co-operation of the psychologist might go far to clarify the association.

DISCUSSION

The relationship between convergence function and the general condition of the patient has been recognised for the past sixty years, since Maddox advised constitutional measures for the treatment of the symptoms. Heath mentioned its association with general conditions and nervous prostration, while the use of strychnine in treatment was described by Oppenheimer.

Bielschowsky and Howe, among others, considered the general health an important relationship to convergence insufficiency. The significance of the endocrine glands has been stressed by Mayer (exophthalmic goitre), Fridenberg, Bryant, Howard (hypothyroidism), Davis (endocrine disorders), and others. Zentmayer mentioned over-stimulation of the body followed by fatigue as a cause of convergence insufficiency, while Duane recommended attention to the general heath after correction of refractive errors. Fox was of the opinion that the condition had a close relationship to the general health, while Field remarked on its dependence on the general physical condition.

Modern writers begin to stress the importance of the psychological state of the patient in the aetiology of convergence insufficiency. Mann considers that an essential factor is arrested development of the function of convergence, and that the majority of patients are normal individuals with an arrested functional

development which only begins to trouble them when they are employed in excessive close work. In older patients psychological difficulties are liable to precipitate the onset of symptoms. This would make an attractive theory, introducing Adler's conception of organ inferiority. It would be necessary, however, to prove that these patients had deficient convergence before the onset of symptoms. Others assign to psychological factors alone a more important role in the aetiology.

There is a similar uncertainty and divergence of views on the permanent effects of orthoptic treatment. Abraham considers that orthoptic training can be of palliative value only, and that the continual exercise of convergence during the waking hours should be expected to be more effective than a short period of special training, even if given daily. Local exercises he holds to be of little permanent therapeutic value. Others regard convergence at the near point as a trick that can be learned with practice. The majority of writers, however, agree that considerable immediate benefit and cure can be obtained in a large proportion of cases by orthoptic exercises.

The cure of psychological symptoms by physical methods is a well-recognised phenomenon in many branches of medicine, and is not confined to ophthalmology. The influence of suggestion and the personalities of the physician, surgeon, physio-therapeutist or orthoptist may all or individually play the major role. During the course of treatment psychological difficulties may become ameliorated or resolve, with consequent benefit to, or disappearance of the symptoms.

Although in the present investigation cure of the symptoms was always accompanied by improvement in the objective signs, it has been noted by many observers that this is not invariably the case. Disappearance of the symptoms may be accompanied by persistence of, or but slight improvement in the objective signs. This raises the question of the part which suggestion plays in the cure of such cases, and the importance of this factor should not be under-estimated.

That patients can relapse with re-appearance of the typical symptoms, without manifesting any of the objective signs, is also well established. This brings these cases into line with the untreated group which exhibits the classical symptoms without ever having shown any of the signs of convergence defect.

The question of fatiguability of convergence was investigated in several subjects. After their convergence was measured, they were allowed to read till symptoms developed, when the readings were repeated. No appreciable differences were found.

A further point worthy of consideration is whether in some cases the signs elicited, namely convergence deficiency, are suggested to the patients by the method of examination. This is the probable explanation of the expanding and contracting spiral fields of vision found in neurasthenia (Traquair). The extraordinarily rapid progress made by some patients under a skilled orthoptist in the course of one or two " lessons " certainly would make one suspect whether a similar cause operated here.

Summary

The results of treatment of 88 cases of convergence deficiency are described. The question is raised whether convergence deficiency is a psychosomatic manifestation, and suggestions are made for further research.

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A CONTRIBUTION TO THE THEORY OF THE VASCULAR ORIGIN OF GLAUCOMA*

BY

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PRAGUE

INTRODUCTION

IT appears to-day that, after nearly a hundred years of controversy, the solution of the problem of pathogenesis of glaucoma has entered its final phase. The literature concerning this theme was immense. Some of the authors approached the problem with a modern outlook, but Leber's classical theory, with which their results did not agree, could not be rejected. After a time they formed a new conception based on their own observations.

Though the vascular system was often mentioned, the old conception of the pathogenesis of glaucoma remained unchanged. One thing was clear, namely, that primary glaucoma was not a local disease of the eyes, but an eye complication of some organic or constitutional disturbance still unknown (Gordon 1938, Duke-Elder 1945).

It was apparent that the problem of the pathogenesis of glaucoma could only be solved analytically. This method was used in the study of glaucoma, published in 1946. When analysing the origin of hypertension, the anatomical findings, clinical observations and the effects of treatment, the following conclusions were made, glaucoma is the expression of stasis in the venous system and the eye capillaries. It has its origin partly in organic vascular changes with a more or less marked spastic factor and partly in changes in function (vasoneurosis).

When ocular hypertension was analysed, it was clear that the problem was one of the intra-ocular fluid and blood circulation. These problems, which are so closely connected, are identical with the question of the peripheral circulation and of fluid-balance. It is therefore necessary to observe the function of the peripheral arterial circulation in glaucoma. The disorders of the peripheral arterial circulation in glaucoma, as already mentioned, are not only local but general. Some of the authors noticed a possible pathogenic connection with the circulation; on the contrary the majority

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From the first ophthalmic clinic, Director, Professor R. Kadlický, and from the second internal clinic, Director, Professor A. Vančura of the Charles University, Prague.

were satisfied with the old conception. They believed that ocular hypertension caused all the disorders which appear in the evolution of glaucoma, including the circulatory disorders. The word glaucoma and ocular hypertension were synonymous. Nothing changed this belief, not even the so-called glaucoma without hypertension—the disease where the second main sign of glaucoma is predominant, namely, the excavation of the papilla of the optic nerve without an increase in intra-ocular pressure. This form of glaucoma has a long history. It begins with Graefe's " amaurosis with excavation," then the term glaucoma without hypertension and pseudoglaucoma and later the term incomplete glaucoma. It was necessary to change this term, because the excavation which could have its origin in hypertension, can exist without it. Regarding the influence of eye hypertension it was said that the hypertension might be only small or transitory (Donders). No proof could be obtained from anatomical findings, Schnabel (1892-1905), described the lacunar degeneration of the nerve-fibres in the optic nerve with glaucomatous excavation. This condition, which was similar to changes occurring in the brain, was called " status lacunaris " by Pierre Marie. He described vacuoles formed in the optic nerve by the joining of the lacunae, and causing depression of the papilla. The author himself discovered that the causes of these disorders were angiosclerotic retrobulbar lesions, namely lesions of Haller's arterial circle. Thus Schnabel definitely rejected the view of the pressure-origin of excavation. In spite of his clear proofs and the work of his followers, his opinion of the origin of glaucomic excavation is not generally accepted, even to-day (Elschnig, Ichikawa, Langrange, Beavieux, Gallanga, Magitot, etc.). Experimental results and clinical experience are not sufficient. Artificial hypertension produced by ligature of the veins did not give rise to excavation even after five months. Clinical cases are well known where the function of the eye restored by operation, deteriorates progressively, even without hypertension. This might be considered as evidence of disturbed tissue-nutrition.

REPORT OF THE METHODS USED AND OF OUR OWN OBSERVATIONS

When estimating ocular hypertension it is seen that there are problems which are in close connection with the peripheral blood circulation and fluid-balance. As already mentioned, these problems led to our examination of patients suffering from glaucoma, with particular reference to the examination of the cardiovascular system. The colloid osmotic pressure of the plasma-proteins was estimated, and the investigation completed by a series of tests leading to the explanation of the plasma-protein spectrum. The

blood cholesterol and urine were examined, and Wassermann reactions ascertained.

A total of 97 patients were examined: 23 with acute inflammatory, 14 with chronic simple, 37 with chronic inflammatory and 23 with secondary glaucoma.

A. *Examination of the cardio-vascular system*

A statistically important relation was found between vascular hypertension and glaucoma — hypertension being found in our series more frequently than in patients of the same age using the hypertension table of Robertson and Brucer from Vancura. In the group of secondary glaucoma, deviations were not so striking.

Because even the highest diastolic readings are comparatively low, hypertension due to loss of elasticity of the vascular wall can be excluded. Systolic hypertension could be expected in our patients on account of their age, but radiological findings show signs of arteriosclerosis. The ECG showed mostly left ventricular preponderance, which is usually caused by hypertension. Some findings, such as auricular fibrillation, prolonged P-R interval, infarctions and possibly bradycardia are signs of coronary sclerosis.

In conclusion it may be said that glaucoma with hypertension is quite evident in 95 cases where the examination of the cardiovascular system was made. It is not possible to characterize this co-existence more closely. But it can be stated with certainty that the patients of this group suffer from vascular disease.

It is necessary to complete the examination of the peripheral abnormalities of the vascular system by the determination of the oscillatory index and capillaroscopy. Before making the examination a detailed family and personal history was taken for evidence of cardiovascular disease.

Patients suffering from acute glaucoma often complained of paraesthesia of the limbs, *digiti mortui*, cyanosis, intermittent claudication, migraine, hypertension, diabetes, varicose veins and their complications and urticaria, as seen from their personal histories. These complaints confirm the presence of vascular disease. This positive history was more frequent in chronic inflammatory glaucoma (42), than in acute inflammatory glaucoma (22), and in secondary glaucoma (12). Excitability is considered a sign of a labile vascular system by many authors. This was found in chronic inflammatory glaucoma 16 times, in acute inflammatory 10 times, in secondary glaucoma 9 times, and in chronic simple glaucoma only twice.

Oscillation was determined by means of the oscillotonometer in the usual way above the ankle, above and below the knee-joint,

and on the arm. According to Prusík the loss of the oscillatory index to 50 per cent. and more was regarded as a decrease from the normal. The signs which were reasonably supposed to be of vascular origin, were verified by the symptoms of the patients. A decrease in the oscillatory index was found in acute inflammatory glaucoma in 11 cases (12 normal values), in chronic simple glaucoma in 8 cases (6 normal values), in chronic inflammatory in 15 cases (22 normal values) and in secondary glaucoma in 4 cases (19 normal values). In 97 cases a distinct decrease of values above the knee-joint was seen 4 times. This decrease indicated the necessity for appropriate therapy.

When making a critical evaluation of these facts two striking points are seen: decreased oscillations in all groups except secondary glaucoma, and the obvious predominance of this decrease in chronic simple glaucoma.

Capillaroscopy: the capillaroscopic determinations were made by the Zeiss capillaroscopic microscope. The capillaries of the nailrim, the flexor sides of the fore-arm, the outer part of the arm above the olecranon and the left infraclavicular region were examined. From the findings it was possible to estimate the condition of the capillaries.

	Vaso-neurosis	Transitory forms	Arterio-sclerosis	Normal
gl. ac. infl. ...	14	4	5	—
chr. simple ...	2	1	10	1
chr. infl.	16	9	11	1
sec.	6	1	4	12

When making a microscopic examination of the capillaries none of the 23 cases of acute glaucoma gave normal findings. This group showed an absolute predominance of vasoneurosis. In chronic simple glaucoma the relationship is quite different, giving evidence of arteriosclerosis. In chronic inflammatory glaucoma both groups are the same and finally in secondary glaucoma the microscopic findings of the capillaries are mostly normal.

In making a general estimation of the cardio-vascular findings, the most striking thing is the tendency to disease in our patients. The cardio-vascular findings show that the patients with glaucoma often suffer from hypertension with all its consequences and electro-cardiographic findings. X-ray findings show the presence of arterio-sclerosis, which is not surprising, considering the age of the patients. The oscillatory findings indicate anatomical and, considering the age, mostly arteriosclerotic changes in the peripheral arteries. The most common occurrence in chronic simple glaucoma may well illustrate the findings of those authors who

found sclerotic changes in the intra-ocular vessels. The microscopic examination of the capillaries shows the same condition in the smallest vessels. In general our cardio-vascular findings are in agreement with the extensive literature.

B. *Biochemical examination*

The protein spectrum was examined first to estimate the colloidal osmotic pressure from the absolute values of the serum protein. This osmotic pressure, as was known, plays an important part in the formation of the tissue fluid against the hydrostatic blood pressure of the capillaries. It was also necessary to verify the influence of local changes on the plasma-proteins; in this way the importance of other associated illness and their possible aggravation of the increased intra-ocular pressure was seen. The erythrocyte sedimentation-rate was estimated using the Westergren method, and read after the first two hours and after 24 hours. The flocculation test with cadmium sulphate according to technique of Wuhrmann and Wunderly and the Takata reaction were performed and estimated according to these authors. The nephelographic curve was examined instead of Weltmann's coagulation band. But the findings had only a relative value because for technical reasons it was not possible to measure the turbidity by means of the nephelometric arrangement of Pulfrich's photometer. The turbidity was ascertained fluorophotometrically by its transmission of light. The absolute plasma proteins were estimated by the Kjehldal method.

The normal erythrocyte sedimentation rate was 10 mm. for men, 13 mm. for women during one hour.

	Normal	Increased	Not explained
gl. ac. inf. ...	12	11	3
chr. s.	10	4	—
chr. infl.... ...	18	19	2
sec.	18	5	—

We suppose therefore that glaucoma itself does not lead to an increase of the erythrocyte sedimentation rate even in the presence of acute inflammation. When higher values during the first two hours were found these could be nearly always explained by concurrent disease leading to an increased sedimentation rate (inflammatory or degenerative kidney diseases, inflammatory diseases of the urinary tract, diabetes mellitus, arteriosclerosis univ.). This increase was then explained by the primary ocular findings in secondary glaucoma.

The cadmium test was positive in four cases. This cannot be explained by the glaucoma and an explanation similar to that given for the erythrocyte sedimentation rate was suggested. The Takata test was always negative. Its positive result would have indicated the necessity for a further liver investigation.

In nephelogram the most striking change was a shift to the left. A clear shift to the left was seen only once (—2). This could be explained by the general serious condition of the patient where the acute glaucoma occurred with nephrosis, diabetes and severe cachexia. The shift to the left (3,4) was seen 21 times, in 11 cases in chronic inflammatory glaucoma. It is likely that this shift has nothing to do with the glaucoma itself, because it did not occur in 3/4 of the cases. We did not always succeed in finding a connection with other disease. A shift to the right was not noticed. Comparing the heights of our curves we nowhere saw the clear fall which is an unfavourable prognostic sign when considering the general condition of the patients.

The colloidal osmotic pressure was estimated according to the paper of Wunderly and Wuhrmann. We next wanted to determine whether the decrease of the COP was the cause of glaucoma and under which conditions. The normal COP is given as 300-400 mm. H_2O by the above-mentioned authors. This means nearly 22-29 mm. Hg. The decrease below 300 mm. H_2O was found in 33 cases (see the table).

	gl. ac. i.	ch. s.	ch. i.	sec.
Increase	4	3	11	6
normal	10	8	10	12
decrease	9	3	16	5

It is quite clear that the decrease in COP which sometimes occurs in early glaucoma does not play any important part because an increase which would cause quite an opposite reaction was also occasionally noted The lowering of the level of the serum albumin causes the decrease of the COP as seen from Key's formula. This decrease may sometimes be compensated by increase in the globulin level. On reading Bing's paper from 1946 some facts are seen which quite agree with our findings. Bing found hypoproteinaemia in 13 per cent. of 500 patients suffering from internal diseases. The average age of our patients is nearly 60; in the group of simple glaucoma it is much higher (72); at this age a decrease of osmotic pressure as the result of hypoproteinaemia is given in 21.6 per cent. (Bing, 24 per cent). Bing shows hypoproteinaemia according to the sex—16 per cent. male to 11 per cent. female. It is possible to explain our opposite relationship by a greater number of women examined (33 men to 54 women). Applying COP of Bing's patients according to the above-mentioned formula 99 cases of lowered osmotic pressure under 300 mm. H_2O are found in 136 patients. Not one case of glaucoma is mentioned. Sometimes there is also no mention of oedema occurring elsewhere. In the same way Wuhrmann and Wunderly do not show glaucoma as a complication in their patients suffering from hypoproteinaemia amounting to 12-15 per cent. of the normal COP. In this respect we cannot confirm A. C. Krause's findings. The decrease in COP to under 300 mm. H_2O was found only once by him in 20 cases of chronic glaucoma and six times an increase above 400 mm. H_2O was found calculating according to Keys. Clinical experience must also be considered. The amount of albumin decreases in acute infectious diseases and the amount of coarsely dispersed proteins (globulin and fibrinogen) rises. In these conditions the intra-ocular pressure must rise until an equilibrium of the serum proteins is reached. The plasma-proteins are considerably decreased in hypoproteinaemia of different origins (bleeding, nephritis, nephrosis, essential). As a result of this the osmotic blood-pressure is decreased, leading necessarily to an increase in IOP, a fact usually not observed. On the contrary the injection of blood-plasma in patients with diseases associated with hypoproteinaemia should cause a decrease in intra-ocular pressure; this could not be confirmed (Natale). The ordinary medical and operative treatment does not cause an increase in COP. The same proof is given by unilateral eye-affections, although the influence of COP should be noticed on both sides.

Cholesterol was estimated by means of the photo-electric colorimeter so that the level of the total cholesterol and its esters in the serum was obtained. The normal findings are 150-200 mg. per cent. of total cholesterol and 70-150 mg. per cent. of esters. This examination was made to verify Schmelzer's findings. Schmelzer found a definite hypercholesterolaemia in the majority of the examined patients who were suffering from glaucoma. We could not confirm this finding in the 97 patients examined. The decrease in cholesterol esters which was found in all forms of glaucoma was most striking. We searched in vain for an explanation in the literature. It is thought that this decrease in cholesterol esters is related to the changes in cholinesterase and choline (the latter being a lipotropic substance). But this would need a direct proof.

The urine examination. The first morning specimen of urine was examined qualitatively and microscopically. We wanted to know whether disease of the kidney is related to the hypertension occurring in glaucoma. We did not find any connection except some rare cases of diabetes or chronic nephritis confirmed by the history. Inflammatory diseases of the urinary tract often occurred in women.

C. *As a supplement to the blood examination the Wassermann test and the gonoreaction were performed.* Positive results were rare and unassociated with the condition.

Discussion

The examination of our patients suffering from glaucoma showed that the pathological findings were to a large extent lesions of the cardio-vascular system. This confirmed our conclusions about the functional and organic changes in the vascular system. These conclusions are in agreement with the findings of many authors. When the rest of the war literature accessible only to-day is reviewed, and the literature since 1945, many authors are found to agree with the vascular origin of glaucoma. Magitot considers the increase in intra-ocular pressure to be due to an increase in capillary permeability occurring as a result of vascular disease. On the contrary, atrophy of the optic nerve indicates another process, which causes vascular obliteration and lacunar degeneration. This obliteration is probably an anatomical obstruction which is the result of sclerotic narrowing of the lumen of the arteries. The spastic factor contributes in the early stages as in an all vascular processes. Only later are the walls under the influence of obliterative degeneration. Redslob also considers lacunar degeneration of the optic nerve to be the main cause of excavation. Sjögren holds the same opinion. Weekers considered that changes in the ocular vascular system were the cause of glaucoma. The lesions affect the uvea, retina and optic nerve. The three main symptoms of glaucoma correspond to these three localizations: ocular hypertension, loss of the visual field and atrophy with excavation of the papilla. These three symptoms appear generally together but not always. Thus the author deals with the expression of incomplete glaucoma (mono- and bisymptomatic glaucoma). Gérard agrees with Weekers. In the pathogenesis of glaucoma the vascular phenomena are primary—this is said by Venco. Cristini considers that changes in the arteriolar vessels of the uvea are the cause of glaucoma. Morax in his contribution to the study of the pathogenesis of glaucoma considers that the vascular changes which are so constant in glaucoma are the dominating influence.

In the second group there are authors who say that glaucoma is caused by vascular disorders originating in the vegetative centres. To this group belongs L. Hess, who declares that the vascular and circulatory changes in glaucoma are angioneurotic changes due to central irritation. An important part is played by the diencephalic centre at the base of the brain (Karplus-Kreidl). Morreau considers glaucoma to be an oculovascular disorder caused by a disorder in the equilibrium of the sympathetic and parasympathetic system under endocrine influence. According to Marquenze glaucoma has its origin in vascular changes in the anterior and posterior segment of the bulbus oculi. These changes

result from imbalance of the vasomotor nerves. This imbalance is sometimes caused by the thalamus and at other times by the endocrine glands. Zondek and Wolfsohn show that glaucoma is connected with the di-encephalo-pituitary system. Magitot, perhaps influenced by these authorities, especially by Hess, concludes (1947) that glaucoma is not only a disease of the organ of sight but also a disease of the affect (which is far from his original conception). The importance of the central nervous system (either vegetative centres or centres of the autonomic nervous system) on the increase in intra-ocular pressure is emphasized by Podljusak, Fradkin, Levina, Archnagelskij. Lucena considers that general and local vegetative dystonia is responsible for glaucoma.

These papers stress the vascular pathogenesis of glaucoma, and mention the participation of the organo-vegetative system and the ductless glands — partly in isolation, and partly in connection with the autonomic nervous system. Indisputably the autonomic nervous system has an influence, especially through innervation of the arterial walls, but this influence is inconstant and accessory. Sympathetic hypertension helps to promote an ischaemic crisis, just as parasympathetic hypertension discourages local angiospasm but is not able to neutralize it. The di-encephalic centres play an important part in the general regulation and co-ordination of the various autonomic centres as observed in all the higher centres of the autonomic system. Though their importance is considerable they do not always participate. As in all other higher autonomic centres of the cerebrospinal system, a loss in function after the phase of transient damping causes a freeing of activity of the lower centres which will take over autonomy. Failure may be to a certain extent compensated by the activity of the lower centres. This was proved experimentally, and many clinical observations also confirm it, *e.g.*, extensive destruction of the di-encephalic sphere (by tumour, inflammation, etc.) were associated with no autonomic symptoms. In two cases Cushing removed the whole infundibulo-tuberal area, but he saw no important signs (Tinel).

It is evident that some authors explaining the influence of emotion on glaucoma failed to mention the activity of important intra-mural centres. There is a new danger that we shall not succeed in discovering the pathogenesis of glaucoma. The final explanation of the whole problem will be again postponed. Surely the autonomic centres have an influence, but these are the peripheral and intramural centres which form with the vessel together an anatomical and functional unit. Only in this sense it is possible to speak about the influence of the autonomic system in glaucoma.

Many syndromes can appear as well as increased and decreased

irritation of the central regulative systems. Syndromes showing excessive activity or functional inactivity of some peripheral autonomic centres do not depend on functional changes in the sympathetic or parasympathetic system. The changes in activity are brought about directly by disorders of the mural systems. This increased or decreased irritation can be constitutional, congenital and hereditary. Other conditions associated with increased irritation are certainly acquired. This acquired increase of irritation has different causes: (1) repeated reflex excitation (approximating to conditioned reflexes); (2) humoral, autotoxic causes, perhaps in connection with slight renal and hepatic insufficiency, intestinal intoxications, arthritic diathesis, etc.; (3) glandular causes, *e.g.*, Graves' disease, puberty, menopause or the menstrual cycle; (4) anaphylactic manifestations; (5) psychological disorders, especially emotion. These different factors nearly all lead to the activity and fixation of the different active or paralysing substances on the automatic nervous centres (Tinel).

It is the increased and decreased irritation—namely, dystonia of the autonomic vascular intramural system—which enables us to explain the signs occurring in the course of glaucoma, the so-called inflammatory signs, especially in young subjects where we cannot expect structural vascular lesions. It is similar to the simple vasomotor syndromes of other peripheral arteries, especially Raynaud's disease, which is a vasomotor neurosis in which spasm plays a primary part. Sclerotic vascular lesions are found only in the later stages of the disease as a consequence of prolonged vasomotor ischaemia. These lesions complicate and aggravate the syndrome, making the changes irreversible. According to Claude, it is one of the most striking examples of a change from a functional, dynamic and paroxysmal lesion into an organic, permanent and irreversible syndrome (Tinel). There are also cases where the spasm is secondary to a primary arterial lesion. In these cases there is a more marked narrowing of the vessels. It is generally known that angiospasm is associated with arteriosclerosis. The familial occurrence of inflammatory glaucoma, the marked incidence of glaucoma in certain families, the appearance of acute crises and their spontaneous disappearance, the effect of temperature, the influence of emotional factors all suggest a spastic factor. Some clinical manifestations are otherwise quite unexplainable; *e.g.*, the crisis of transitory amblyopia, the changing of scotomata and all the disorders which subside after disappearance of the inflammation. On the other hand, chronic simple glaucoma which tends to come later and to get progressively worse is probably the result of a predominantly anatomical lesion.

From this point of view it is necessary to understand the influence of the endocrine glands. Glaucoma rarely occurs as an early or late complication of disorders in endocrine function. When glaucoma and endocrine disorders occur together, either hyper- or hypro-function of the endocrine glands may be present. The disorders of hyper- and hypo-function — *i.e.*, the quantitative disorder—are not always the cause of endocrine disorders, but more often dysfunction—a qualitative disorder. The influence of the intramural autonomic vascular apparatuses on changes of irritability can be compared to the last drop which causes the glass to run over.

Finally, secondary glaucoma should be mentioned. Previously when workers have sought for the pathogenesis of glaucoma they have considered the primary and secondary forms as two distinct diseases. We consider that this view is incorrect. The difference is this: In primary glaucoma the primary lesion is the vascular disease, functional or organic; but secondary glaucoma is caused by other ocular lesions. The mechanism of origin may be the same. In the peripheral arteries we found signs not only of vasoneurosis, but also of arteriosclerosis. But not all secondary glaucoma is caused by these disorders. In some cases the influence on the vessels is direct, and after cessation of this the glaucoma spontaneously disappears. The most typical instance of this is acute serous iritis. The vascular disease is not primary in this case, as is confirmed by the fact that the ocular function is not injured when the glaucoma lasts a long time. Secondary glaucomas show only an increase in intraocular pressure. This is a proof that hypertension does not lead to the functional loss of the eye. On the contrary, there are diseases which cause ocular hypertension. These diseases, based on axon-reflexes, can in time lead to a functional condition which develops into an organic lesion with all its consequences. Ultimate loss of ocular function is not only due to changes in the vessels of the optic nerve, which lead to changes in the integrity of the nerve fibres. Nutritional disturbances play an important part. They have their origin in the damaged circulation of the choroid. Glaucoma during thrombosis venae centralis retinae occupies a special place in this category of secondary glaucoma. We know that it does not often occur. In the literature secondary glaucoma is mentioned as a complication in 20 per cent. of cases, but is this a true secondary glaucoma? It would seem that the same vascular lesions which lead to thrombosis cause glaucoma. The simultaneous appearance depends on the localisation of these lesions (retina, choroid).

The result of work on the estimation of acetylcholine, histamine, cholinesterase and amino-oxydase in the aqueous humour and blood-serum in patients suffering from glaucoma are not yet numerous, but indicate a vascular genesis. Bloomfield found a substance in the aqueous humour influencing the parasympathetic system 17 times in 20 normal eyes.

In 7 cases acetylcholine was found, in 3 cases the substance was not acetylcholine. On the other hand the result was negative in 20 glaucomatous eyes. A feebly active parasympathicomimetic substance was found only 5 times. He concludes that this cholinergic lack is related to glaucoma. A substance was found by Halbertsma in the aqueous humour of glaucomatous patients. This substance was similar to histamine, judging by its effect on the vessels of the guinea-pig. This agrees with the previous findings of Chopra and Ridley regarding epidemic dropsy.

Bruckner (1943) was the first to consider the problem of cholinesterase. He was also the first to find cholinesterase in the aqueous humour of man. He does not consider that cholinesterase has its origin in blood. Esterase in the vitreous probably comes from the retina. In another work he determines the level of esterase in isolated eye tissues. Rados (1943) was the first to estimate the level of esterase in the blood of patients with glaucoma. In glaucoma its level is not different from the normal. On the contrary an increase in the serum level of cholinesterase in some patients suffering from glaucoma was found by Gallois and Herschberg. Thomas, Verain, Cordier, Henry (1946) have inconsistent results in estimating the level of the blood cholinesterase. They did not find cholinesterase in the aqueous humour or in the plasmoid. But Vidal and Malbran (1946) found an increase in cholinesterase in the aqueous humour in patients suffering from chronic glaucoma.

Our conception of glaucoma has therefore changed very much during the last few years. Two fundamental things are necessary: a careful diagnosis of glaucoma and the revision of our treatment. These are the problems with which we must concern ourselves.*

* We wish here to express our sincere thanks to Prof. J. Horejši, the director of the biochemical laboratory of the First Internal Clinic of Prof. K. Hynek, for enabling this work to be carried out and for his useful advice.

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BOOK NOTICES

The Practice of Orthoptics. By G. H. GILES. F.B.O.A. (Hons.), F.S.M.C. Hammond, Hammond and Co. Ltd., London. 1949. 30/-.

This book contains useful information with regard to the selection and care of cases of strabismus suitable for orthoptic treatment. There is, however, a lack of appreciation of the scope of early surgical treatment.

The author states in discussing the treatment of concomitant convergent strabismus in children that "where the squint is alternating and the vision equal in both eyes, the squint can be safely left, provided due care and attention are paid to the refractive error. The patient reports periodically for exercises, but as a rule no orthoptic treatment is given until the child can appreciate what is meant by "mental effort." This may be all very well if there is some contra-indication to operation on general grounds, but if such a procedure is universally adopted it means that the squinting child is left to battle with the adverse psychological effect that his physical deformity may cause, and is allowed to consolidate the secondary sensory and motor correspondences which subsequently may prove so difficult to remove. In the case of squint, as in any other physical deformity, an attempt should be made to cure the condition forthwith, not only cosmetically but also functionally.

The chapter entitled "The selection of Orthoptic Cases of Strabismus" is good and clearly set out, but it would have been better entitled "The selection of Cases of Strabismus for Orthoptic Treatment."

The section of the book dealing with practical lines of treatment is good, and it is refreshing to find that Mr. Giles appreciates the value of simple forms of apparatus. It is a pity that the author, although realising that ocular palsies are outside the scope of the book, has included two misleading diagrams (Figs. 16 and 21) which are intended to show the actions of the extrinsic ocular muscles. It ought to be recognised by now that the vertically acting recti

muscles, although they are adductors, produce their maximum vertical action when the eye is abducted. Similarly, although the obliques are abductors, they produce their maximum vertical action when the eye is adducted.

The statement on page 68 that it is rare (in cases of ocular palsy) to find only one muscle affected, probably indicates a lack of appreciation of the occurrence of the sequelae that take place following palsy of a single extrinsic ocular muscle.

The value of mental effort in the treatment of strabismus is undisputed, but one would have preferred to see photographs, such as Fig. 35, which purport to show the effect of mental effort in the case of convergent strabismus, explained on a physiological rather than on a psychological basis, *i.e.*, that when the eyes are elevated and accommodation is relaxed, the visual axes tend to diverge.

The practical advice given with regard to the use of various orthoptic instruments is excellent and there is interesting information on orthoptic treatment for candidates for flying duties, and on naturopathic methods of treatment.

The author is to be congratulated on the detailed bibliography given at the end of the book.

An Introduction to Clinical Perimetry. By H. M. TRAQUAIR, M.D., F.R.C.S. Ed.

Comparison between the sixth and fourth editions of this well known work shows that comparatively few additions have had to be made in the text or in the illustrations, and from memories of the first edition, the same observation would probably be true, were it to hand. In other words, when "An Introduction to Clinical Perimetry" first appeared, it had been so carefully written that after the lapse of 22 years, only a few changes were needed to bring it up-to-date. It is not surprising therefore that Traquair's book should have achieved international fame as the outstanding authority on perimetry.

The changes in the present edition comprise revision and amplification of the text, and the inclusion of two new illustrations and of two coloured plates, one from a case of Mr. Keith Lyle's showing medullated nerve fibres indicating the course of the arcuate fibres in the retina; the other plate illustrating a chiasmal tumour. A short allusion is made in the text to Goldmann's spherical perimeter, in which it is stated that "its clinical advantages have yet to be determined." Although the author is well known as an advocate of non-mechanical perimetry, readers of the new edition of his book might have welcomed his considered opinion of an instrument which may have a big future in clinical work, and about which some articles have appeared in the foreign press. The same is true of projection scotometers which have several advantages in mapping-out central defects on the screen. These are only minor points, however, and

where such admirable work has been done with the simple instruments favoured by the author it may seem almost invidious to suggest any others. Not all ophthalmologists, however, are gifted with the skill and patience of Mr. Traquair, and if new methods of field-taking make the task any easier or more accurate in less practised hands than his, they are to be welcomed, but not until they have been tried and tested by a master of the art.

Towards the end of the book, there is an interesting new paragraph on the scotoma of amblyopia *ex anopsia* which did not appear in the fourth edition, and gives the means of distinguishing what is really a functional scotoma from the organic one, due say to a small patch of central choroido-retinitis, which is occasionally the cause of the supposed amblyopia.

In advertising a well-known tobacco, the firm concerned distributed trays bearing the legend, "You cannot have too many ash-trays," and after reading Clinical Perimetry, one feels inclined to plagiarise and say "You cannot take too many fields."

Mr. Traquair has, we hope, made the English-speaking world field-conscious, and conscious not only of the necessity for taking fields but also of the necessity for using quantitive methods in doing so.

CORRESPONDENCE

To the Editorial Committee of

THE BRITISH JOURNAL OF OPHTHALMOLOGY

DEAR SIRS,—Dr. Lewis Németh states in his article on the use of anti-histamines locally in allergic conditions of the eye (*B. J. O.* November, 1949), that Antistin Privine drops have proved of great value in several conditions. In my experience the symptomatic relief which has been obtained in most of these conditions is due entirely to the Privine content of the drops. Messrs. Ciba very kindly supplied me with samples for clinical trials of Antistin drops alone and I found these, when used without oral administration of an anti-histamine, to have no action whatever either in the relief of symptoms or in the cure of the condition. In one bad case of hay-fever I switched the drops from Privine only to Antistin only, two or three times with the patient's knowledge. The first drops gave immediate symptomatic relief, the second gave no result whatever. I believe that in Privine we have a most useful therapeutic weapon, and a most pleasant form of drops for the patient to use (very different from adrenalin in this respect). In welder's flash, reflex congestion from eyestrain, and in hay-fever (in this latter condition it should be used in conjunction with anti-histamines by mouth), it is superior in every way to Adrenalin or like compounds.

I am, Sir, your obedient servant,

BIRMINGHAM, *November* 8, 1949. L. H. G. MOORE.

To the Editorial Committee of

THE BRITISH JOURNAL OF OPHTHALMOLOGY

DEAR SIRS,—Messrs. Klein and Miller are to be congratulated on their interesting and informative paper (*B. J. O.* October, 1949), drawing attention to the value of urea in the treatment of dendritic keratitis. They are not quite correct, however, in saying that urea "has not been employed in ophthalmology." Urea was introduced to the Portsmouth Eye and Ear Hospital by Mr. W. Hedley Summerskill over two years ago, for the treatment not only of herpetic keratitis but of other ocular infections of an assumed virus origin. The rationale for its employment, given by him, was that the virus molecule disintegrates in the presence of urea throwing off its SH groups and becoming inactive. The urea has been used as 50 per cent. drops 3-hourly in sterile aqueous solution (*i.e.*, a saturated solution). Such a solution is stable, compatible with atropine sulphate and has proved non-irritant to the eye. For intra-ocular infections 200 grains have been given by mouth daily.

It is gratifying to have had the value of urea treatment confirmed and published by Messrs. Klein and Miller. Results at this hospital have been encouraging and satisfactory in view of the obstinate cases in which it has been employed. As an adequately controlled comparison with other treatments had not been undertaken, one was hesitant in assessing its value.

Yours faithfully,

PORTSMOUTH, *October* 21, 1949. REX PARISH.

OBITUARY

SIR HERBERT LIGHTFOOT EASON, C.B., C.M.G.

HERBERT EASON will be best remembered by Guy's men of 1920 and after as Superintendent, and by an earlier generation as Dean. Though all knew him as one of the ophthalmic surgeons to Guy's everyone realized that "eyes" played a relatively small part in his activities. Nevertheless he had the reputation of being an outstandingly good lecturer and a most skilled operator. Eason himself would have been the first to admit that his ophthalmic work, hospital and particularly private practice, took second place to his administrative responsibilities.

To the profession as a whole Eason was best known as President of the General Medical Council, while in academic circles he was remarkable as having held successively the posts of Vice-Chancellor and Principal Officer of London University. In his public life Herbert Eason was punctilious to a degree, every letter was answered

promptly, and before every committee meeting he had the agenda at his finger-tips, and was in his seat many minutes before the meeting was due to start. For years while Superintendent of Guy's it was possible to set one's watch at 9.0 a.m. by his arrival in the office.

Eason was one of the most broadminded and tolerant of administrators. He always stressed his accessibility to those, such as house-officers, who were responsible to him. When any difficulties

SIR HERBERT LIGHTFOOT EASON

arose regarding either their private lives or their patients, innumerable house-officers and others at Guy's over nearly twenty years went to Eason and found a real friend and adviser.

As Superintendent he lived in a beautiful Georgian house in the front quadrangle, and many of the Guy's staff, junior staff and housemen will look back with pleasure on the hospitality of Eason, his wife and daughters. He greatly appreciated good food and wine. He had a happy gift of mixing well at parties with those far younger than himself, and no Guy's Ball or other function was complete without the "Super" and his wife. At week-ends he not infrequently used to stay at Huntercombe Golf Club, where he soon became a close friend of Lord Nuffield, a most generous benefactor to Guy's during Eason's regime as Superintendent.

Eason was a superlatively good public speaker, whatever the circumstances. As an after-dinner speaker he was delightfully witty, and seemed to speak equally well even when he was called on quite unexpectedly. At more serious gatherings, such as meetings of the School Council or the Governors, he showed a dialectic skill which completely demolished the arguments of those who held opposing views to his own. He had a biting tongue, and at times caused offence by his remarks about those whom he regarded as pompous and insincere. From the point of view of worldly advancement his quick and mordant wit undoubtedly stood in his way, but his temperament was such that he sometimes found it difficult to curb his tongue.

It is difficult to understand how anyone as methodical as Eason in his public life could have been so different in private life. Letters habitually remained unanswered, and those who came to consult him professionally sometimes found that he had forgotten their appointments, or at best he was late. He was equally careless about sending out accounts. The writer well remembers meeting a rich man who refused to see Eason again, because three written requests for an account had produced no reply.

As President of the General Medical Council, Eason was greatly interested in medical education. Only a few years before his death he went to the United States with other members of the General Medical Council to visit the Medical Schools in that country. At Guy's one of his most popular lectures to students was on the powers and functions of the General Medical Council. In this he used to warn his audience of the dangers of the three A's—Abortion, Advertisement and Adultery. In the hearings at the General Medical Council he was scrupulously fair, and as broadminded as was consistent with upholding the dignity and position of the profession.

Herbert Eason's death is a sad blow for Guy's. Until shortly before his death he attended regularly the meetings of the Board of Governors, where his wise counsel and unrivalled knowledge of the history of the Hospital were of the greatest value.

J. J. C.

O. G. M. writes:—

Sir Herbert Eason would, I feel sure, have been the first to agree that ophthalmology took second place in his life's varied activities, but, as one would expect, he was a master in certain aspects of his speciality.

He was my chief when I was an ophthalmic dresser, and later a registrar at Guy's Hospital, and it was a real stimulus to see his keen assessment of clinical cases. He never shirked his full share of the teaching and refractions in the somewhat tedious over-crowded out-patients of those days. He was an expert operator, and being a musician he had the perfectly controlled hands for this delicate work—quick, sure, and no fussing about; attributes which I usually seem to note in those who get the best results. As a lecturer to undergraduates he was almost unequalled, and his lectures were always fully attended, as were those intensely interesting ones which he used to give more recently on the G.M.C. or other aspects of medical ethics. He spoke so clearly, and could always be relied upon to provide some humour out of the dullest subject.

He published little, but he was keenly interested in new ideas. He never had a large private practice, but was very much in demand for compensation and other Court cases. Insurance companies welcomed his help and much appreciated his distinguished presence, and his remarkable ability to marshall the facts, and put the whole problem in a nutshell. When he had done this, there never seemed very much point in continuing the discussion.

One cannot help feeling that, if he had concentrated his energy and ability on ophthalmology, he would have risen to the highest eminence, but he chose administration, which is perhaps a more uncommon gift in medical men.

NOTES

N.O.T.B. Association

THE Annual General Meeting of the N.O.T.B. Association will be held at 5 o'clock on February 10, 1950, in B.M.A. House, Tavistock Square, W.C.1.

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Ophthalmological Society of Egypt

THE Annual Meeting of the Ophthalmological Society of Egypt will take place at the Memorial Ophthalmic Laboratory, Giza, Egypt, on Wednesday and Thursday, March 15 and 16, 1950, at 9 a.m. The symposium will be the *Sympathetic Ophthalmia*. Medical practitioners, oculists or otherwise, are cordially invited.